VOLUME 60 NUMBER 4

ARCHIVES
OF
DERMATOLOGY AND SYPHILOLOGY

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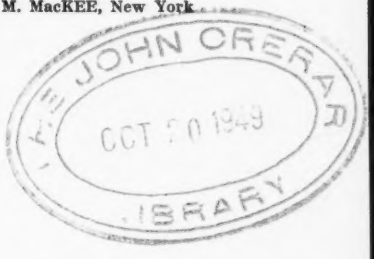

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Editorial Note

At last the issues of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY are current. Differences with the printers' union and inability to obtain sufficient editorial help have made the past year difficult.

Miss Jewel Whelan, who was complimented at the last convention for her many years of service to the Association, has found it necessary to withdraw from the position of Assistant to the Managing Editor. Her unstinted efforts and the valuable part she played in the preparation of the ARCHIVES are greatly appreciated. Dr. Richard J. Plunkett will now be in charge of the production of the ARCHIVES, having recently been made Managing Editor of Special Publications of the American Medical Association.

The present plan is to resume the publication of abstracts of dermatologic meetings in the near future. It is hoped that a supplementary issue limited to transactions may be published this fall. The use of color in photomicrographs and in other illustrations is not as yet possible except on rare occasions, because of the prohibitive cost.

Our thanks are expressed to our readers, who have tolerated the delay in the appearance of the ARCHIVES during the past months, and to our contributors, who have waited months for the publication of their articles with only an occasional objection.

THE EDITORIAL BOARD.

Archives of Dermatology and Syphilology

VOLUME 60 OCTOBER 1949 NUMBER 4

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PRESENT STATUS OF DERMATOLOGIC TRAINING IN THE UNITED STATES

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AND
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FROM the many signs, it would seem that dermatology is at the crossroads. In common with other medical specialties, it has progressed a long way, but it cannot remain static. The future must of necessity be one of expansion. The time has now arrived when those specializing in this branch of medicine must consider seriously the direction of further growth. It would appear logical at this time for them to examine the record of past and present performance in order to help chart an enlightened course for the future. Perhaps in this way some of the pitfalls and errors of this and preceding generations may be avoided. The records of the American Board of Dermatology and Syphilology have been carefully scrutinized; the opportunities for training, together with the background of the chiefs of service of approved institutions, have been analyzed; the present methods of teaching have been considered, and the performance of certified specialists has been evaluated. In addition, the present distribution of certified dermatologists in the United States has been determined. On the basis of the inequalities found, recommendations will be made.

GROWTH OF MODERN AMERICAN DERMATOLOGY

When the American Board of Dermatology and Syphilology was formed in 1932, there was only a handful of graduate training centers for the teaching of dermatology and syphilology in the United States. In 1940, when the first list of approved institutions was published, only 20 institutions were included. Today, there are 80 institutions approved jointly by the Board and by the Council on Medical Education and

Read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 24, 1948.

From the Department of Dermatology, Research and Educational Hospitals, University of Illinois College of Medicine, and the Department of Medicine (Dermatology), New York Hospital and Cornell University Medical College.

Hospitals of the American Medical Association as qualified to teach graduate students for periods of from one to three years. The American Board of Dermatology and Syphilology has now certified 1,001 candidates in the United States, Canada and Cuba. If present trends continue, the already large number of experts will increase even more rapidly during the next few years.

An examination of the record shows that 40 per cent of the present chiefs of service in the 80 approved institutions received their training —and with it the inspiration to become leaders in their field—from four men, namely, Dr. George M. MacKee, Dr. Udo J. Wile, Dr. John H. Stokes and Dr. Harold N. Cole. Without disparagement of the attainments of others in this respect, these four men may be said to have affected profoundly the progress of the specialty in this country.

SURVEY OF APPROVED INSTITUTIONS

Of the 80 institutions now approved for graduate training in dermatology and syphilology, 31 are approved for the full three year training, 26 are approved for two year residencies, 15 are approved for one year training and 4 others have emergency approval for one year. Three institutions are approved for one year of training in syphilis and 1 for one year of training in pathology. One year of postgraduate instruction is given in 4 institutions. With the exception of a school year of basic science in a few medical schools, the Board has not recognized postgraduate training for fractional periods of a year.

For the most part, the program in these approved institutions emphasizes informal teaching, with stress on supervised case study, laboratory work and informal conferences. Fundamental research by students in training is seldom possible, except in three year institutions with small enrolment or in places where there exists a close rapport with basic science departments of medical schools. Formal, didactic courses have been given impetus in recent years because of the large number of candidates from the Services. An analysis of the records shows that this type of instruction is inferior to the more personal, informal training, which stimulates the initiative and individual ability of the student. Close, personal supervsion of the student in training by either the chief of staff or well trained associates is a necessity for the best results. Needless to say, the chief is responsible not only for the development of superior clinical dermatologists but also for the encouragement of constructive and independent thinking.

In an analysis of 10 three year institutions having the largest number of applicants for the Board certificate, the average marks of the candidates from the separate institutions were seen to vary from 83.7 to 77.8. It did not appear that a person having a high grade was necessarily superior with respect to future leadership and scientific attain-

ment, but only that he had amassed a large amount of factual knowledge. Superior rating in the examinations did not necessarily indicate the possession of exceptional reasoning ability. However, consistently inferior grades in an institution are presumptive evidence of poor selection of candidates, faulty program and/or a lack of inspirational leadership by the chief of staff.

Deficiencies in the examination were further investigated by an analysis of the percentage of failures in individual subjects in the various institutions (table 1). As can be readily seen, the teaching of pathology is inadequate in the majority of institutions in the United States. There is also apparent a spotty deficiency in the instruction of certain other subjects. In a further analysis, the average number of subjects failed by candidates from the various institutions was determined. With the exception of 4 hospitals, the subject-failing rate in the

TABLE 1.—*Percentages of Failure, by Subjects, of Candidates Trained in 10 Different Institutions*

Institution	Percentage of Failures in One Subject or More	Percentage of Failures, by Subject						
		Clinical Cases	General Dermatology	Syphilis	Pathology	Mycology	Allergy	Physical Therapy
A	53.8	8.0	8.0	8.0	53.8	23.0	...	23.0
B	41.0	2.5	2.5	18.0	25.3	2.5	5.0	5.0
C	39.0	11.0	6.0	11.0	24.0	6.0	2.5	6.0
D	31.0	2.4	...	4.8	21.9	...	...	9.7
E	28.0	2.3	2.3	7.0	16.2	4.6	2.3	...
F	28.0	12.5	9.7	3.1	6.2	3.1	...	9.7
G	21.0	...	...	...	18.4	2.6	...	2.6
H	19.5	7.4	...	2.4	12.0	4.8	...	4.8
I	19.0	14.3	4.7	4.7	14.3	4.7	4.7	...
J	16.6	6.2	6.2	4.1	10.4	8.3	2.0	2.0

institutions approved for three year training averaged between 1.0 and 1.5 for each failing or conditioned candidate. In the 4 excepted institutions, the subject-failing rate by this group of candidates was between 2.3 and 2.5, indicating substandard training in several subjects.

CHIEFS OF INSTITUTIONS

There are 63 certified specialists of the American Board of Dermatology and Syphilology who are chiefs of service in 77 of the 80 institutions approved for graduate training; the remaining 3 chiefs are not dermatosyphilologists. Of the 63, 30 were in the founders' group and 33 took the examinations. The average mark of the latter group was 83.6, which was only slightly better than that of the B candidates (aged 25 to 35), 83.2.

It is of interest that 25 per cent of the chiefs had a background of general practice averaging 4.4 years; for the most part, their total training was of shorter duration than that of the remainder of the chiefs. In some instances, proficiency in the specialty was acquired

by part time work in clinics over a period of years. Most of the chiefs who had been in general practice were admitted as founders; for the 7 who took the examination, the average mark (80.4) was below the average for all the chiefs who were so tested.

Fourteen of the chiefs had received some foreign training; for 4 the training had been exclusively foreign. In some instances the available data did not include the specific length of training, but it was estimated that the average length of instruction was two years and two months. Some 70 per cent had received their training in a single institution. Over 50 per cent had been trained in one of 7 leading institutions. While the longer the training, the better the prospect of prominence in the field, several chiefs of service who had had short terms of formal training are notable exceptions. Seniority, sole availability and opportunism may have been responsible for some of the appointments, but most have been due to superior ability and initiative. It is significant that only 8 per cent of the 63 are engaged in full time work in hospitals and universities. The remainder are part time practitioners, with a considerable variation in the amount of time spent in the institutions. In general it would seem that success in training men does not depend merely on constant attendance but rather is due to a combination of high ideals, superior intelligence, ability to inspire students and insistence on continued effort and development.

EVALUATION OF CANDIDATES

There has been some criticism of the Board because students are said to study with the sole object of passing the examinations. It would appear that this criticism is not justified. It is no doubt true that many students are of such mental stature that the desire to become proficient would serve as a sufficient incentive. It is also indisputable that many graduate students lack initiative and, unless there is a definite objective, such as the examinations, will not work as assiduously as otherwise. It is our belief that pointing for the examinations has a salutary effect on the average candidate and results in an increased factual knowledge of the specialty. It must be considered the responsibility of the chief of service to teach students to think. Students are later expected to meet minimal standards of competence in the theoretic and practical aspects of the specialty, but preparing for the examinations should not interfere with their development.

A comparison of A candidates (those in the specialty for ten years) with the B group (persons with three years of training) revealed little or no difference in the performance, provided that the same age levels were compared. However, a candidate over the age of 46 had an average mark of 78.3, while B candidates 35 years of age or younger had an average mark of 83.2. The rate of failure was slightly higher in the older age A group (table 2).

A survey of the subjects failed by 211 candidates [1] is shown in table 3. This indicates a relative deficiency in the teaching of pathology in most institutions. The poor results noted in examinations on clinical dermatology were seen predominantly in candidates who received their clinical training largely by didactic methods. There was also some indication that the teaching of syphilis and, to a lesser degree, of physical therapy and mycology is deficient in some institutions

TABLE 2.—*Comparison of Average Marks of A and B Candidates* at Various Age Levels*

Age	A	B
25-35	....	83.2
36-45	81.0	79.7
46 +	78.3	....

* Data are based on study of a sample of 244 candidates.

TABLE 3.—*Relative Frequency of Failure, by Subjects, for 211 Candidates*

Subject	Number Failing	Percentage Failing
Pathology	134	63.0
Clinical cases	53	24.0
Syphilis	47	22.0
Physical therapy	43	20.0
Mycology	37	17.0
General dermatology	30	14.0
Allergy	14	6.5

TABLE 4.—*Grades Made by Students with Varying Amounts of Training and Under Preceptors**

Under Preceptors	Total Amount of Training		
	Less than Two Years	Two to Three Years	Over Three Years
None	76.7	81.2	82.6
1 to 6 months	81.2	77.7	82.0
1 year +	80.4	79.8	82.1

* Data were gathered from a study of 178 candidates.

The candidates who received part of their training under preceptors did as well in the examinations as those receiving hospital training only, when the total period of training was prolonged. This observation would suggest that factual knowledge may be obtained equally well with part time preceptorship as with full time institutional work (table 4), as long as the candidate receives a total of at least three years of training.

1. This group includes all candidates conditioned or failed and an additional sample of those who were given passing marks despite deficiencies in single subjects.

DISTRIBUTION OF CERTIFIED SPECIALISTS

The number and concentration of certified dermatologists in the larger cities of the United States is shown in table 5. It would appear that Washington, D. C., is in greatest supply. However, a fair analysis is difficult, as many of the cities have had nothing short of phenomenal increases in population since 1940, the date of the last census. Consequently the per capita distribution shown may be grossly in error. It

TABLE 5.—*Distribution of Certified Specialists, by Cities, in December* 1947

City	Number of Certified Specialists	Population (1940)	Per Capita Distribution
New York	193	7,454,995	1:38,632
Chicago	50	3,396,808	1:67,936
Philadelphia	33	1,931,334	1:58,525
Washington, D. C.	31	663,091	1:21,370
Los Angeles	28	1,504,277	1:53,709
Boston	22	770,816	1:35,037
Cleveland	20	878,336	1:43,916
San Francisco	19	634,536	1:33,396
Detroit	17	1,623,452	1:95,497
Pittsburgh	15	671,659	1:51,510
St. Louis	14	816,048	1:58,289
Baltimore	12	859,100	1:71,591
New Orleans	11	494,537	1:44,957
Cincinnati	9	455,610	1:50,623
Denver	9	322,412	1:35,823
Milwaukee	9	587,472	1:65,274
Minneapolis	8	492,370	1:61,546
Newark, N. J.	8	429,760	1:53,720
Portland, Ore.	8	305,394	1:38,174
Buffalo	7	575,901	1:82,271
Dallas, Texas	7	294,734	1:42,104
Kansas City, Mo.	7	399,178	1:57,025
Oakland, Calif.	7	302,163	1:43,166
Atlanta, Ga.	6	302,288	1:53,381
Birmingham, Ala.	6	267,583	1:44,597
Houston, Texas	6	384,514	1:64,085
Oklahoma City	6	204,424	1:34,070
San Diego, Calif.	6	203,341	1:33,890
Indianapolis	5	386,972	1:77,384
Richmond, Va.	5	193,042	1:38,608
San Antonio, Texas	5	253,854	1:50,770
Total	589	28,059,991	1:47,640

is obvious, however, that there is a disproportion in the number of certified dermatologists per capita in various cities. Specifically, New York has twice as many dermatologists per capita as has Chicago, which, in turn, is proportionately much more heavily supplied with specialists than are many other large cities. It is clear that the saturation point is near in some centers and equally clear that several other cities may yet support additional dermatosyphilologists. It is of further interest that the 589 dermatologists in these thirty-one cities comprise

69.1 per cent of the total (852) now practicing in the United States. Since the ratio of population of these thirty-one cities to the total population of the United States is 21.2 per cent, it will be seen that 69.1 per cent of the total number of certified dermatologists are serving only 21.2 per cent of the people in this country.

The location of physicians who graduated from foreign medical schools and are now practicing dermatology in the United States is a matter of interest. The total number in this group is 83. Of these, 53, or 64 per cent, are located in New York city. Thus, more than 25 per cent of certified dermatosyphilologists in New York city graduated from foreign medical schools, and most of these persons are of foreign extraction as well. Seven per cent of the group settled in Chicago; 3 of them are in San Francisco; 2 each are in Boston and Los Angeles, and the other 17 of this group are scattered throughout the country.

There are 37 women who are certified specialists of the American Board of Dermatology and Syphilology. Of these, 18, or nearly 50 per cent, are in New York city or its environs, 5 are in Chicago; 2 each are in Los Angeles and San Francisco, and the remaining 10 are scattered throughout the country.

The number of dermatologists certified by the American Board of Dermatology and Syphilology, by state and geographic divisions, is given in table 6. The concentration of dermatologists in the Middle Atlantic States is seen to be twice that of the Pacific region and of the East North Central geographic regions, which are second and third, respectively. On the contrary, the per capita distribution of dermatologists in the East South Central and in the Mountain regions of the United States is grossly inadequate. The West North and South Central areas and the South Atlantic region are also in need of additional dermatologists.

A further analysis of the data regarding the distribution of dermatologists in smaller cities in most parts of the country showed that the relative number of dermatologists was much smaller there than in larger centers. It would be most desirable, therefore, for new certified specialists to consider seriously the advisability of settling in smaller communities. In spite of the lamentable shortage of qualified dermatologists in the small and the medium-sized cities, particularly those serving predominantly rural areas, the majority of recent certified specialists start practice in already overcrowded metropolitan centers. The explanation would appear to consist in a desire on their part to be affiliated with a university center, a wish for the availability of medical libraries and society meetings and, perhaps, in many instances, a response to the lure of a large city. Inevitably, the law of supply and demand will force many of these younger men to move to the smaller communities. It is an appealing fact that the need for adequate der-

TABLE 6.—*Specialists Certified by the American Board of Dermatology and Syphilology as of December 1947, by State and Geographic Divisions*

Section and State	Number of Certified Specialists	State Population (1945)	Per Capita Distribution
New England			
Maine	0	810,415	.....
New Hampshire	1	467,516	1:467,516
Vermont	0	328,554	.....
Massachusetts	27	4,185,282	1:155,010
Connecticut	12	1,794,003	1:149,500
Rhode Island	4	733,186	1:183,296
Total	44	8,318,956	1:189,021
Middle Atlantic			
New York	236	12,817,782	1: 54,312
Pennsylvania	59	9,299,579	1:157,619
New Jersey	35	3,912,236	1:111,778
Total	330	26,029,597	1: 78,877
South Atlantic			
Delaware	4	275,964	1: 68,991
Maryland	13	2,014,387	1:154,952
District of Columbia	31	880,044	1: 28,388
West Virginia	3	1,694,577	1:563,859
Virginia	11	2,937,282	1:267,025
North Carolina	7	3,514,297	1:502,042
South Carolina	4	1,912,960	1:478,240
Georgia	7	3,041,969	1:434,567
Florida	8	2,313,393	1:289,174
Total	88	18,584,873	1:211,191
East North Central			
Wisconsin	12	2,948,262	1:245,688
Michigan	31	5,589,324	1:148,042
Illinois	61	7,486,225	1:122,725
Indiana	10	3,517,277	1:351,727
Ohio	47	6,858,785	1:145,931
Total	161	26,399,873	1:163,850
East South Central			
Kentucky	4	2,598,393	1:649,598
Tennessee	8	2,822,959	1:352,869
Mississippi	3	2,126,175	1:708,728
Alabama	7	2,710,601	1:387,228
Total	22	10,258,128	1:466,278
West North Central			
Minnesota	18	2,630,157	1:146,119
Iowa	5	2,391,213	1:478,242
Missouri	12	3,554,466	1:296,205
North Dakota	1	517,388	1:517,388
South Dakota	0	544,089	.....
Nebraska	6	1,229,674	1:204,945
Kansas	2	1,784,474	1:892,237
Total	54	12,651,461	1:234,286
West South Central			
Oklahoma	8	2,124,250	1:265,531
Arkansas	3	1,851,086	1:617,028
Texas	30	6,696,931	1:223,231
Louisiana	11	2,399,772	1:218,161
Total	52	13,072,039	1:251,385
Mountain			
Montana	0	451,793	.....
Idaho	0	489,164	.....
Wyoming	0	248,753	.....
Nevada	1	142,002	1:142,002
Utah	0	600,692	.....
Colorado	10	1,075,647	1:107,564
Arizona	1	581,586	1:581,586
New Mexico	1	534,248	1:534,248
Total	13	4,123,885	1:317,221
Pacific			
Washington	9	2,162,906	1:240,322
Oregon	8	1,315,676	1:164,459
California	71	9,101,131	1:128,466
Total	88	12,579,713	1:142,610
Total for United States	852	132,018,525	1:156,711

matologic care is nowhere more acute than in these smaller communities, where the young dermatologist has the best opportunity to render a superior service.

STUDENTS IN TRAINING

There are at this time 488 dermatologic trainees in approved institutions in the United States. Provided that the present rate of training continues, approximately 150 new dermatologists may be expected to start practice each year. Even with the normal rate of attrition taken into consideration, the number of dermatologists in the United States in ten years will be more than doubled. The greatest need at this time, then, is for dermatologists trained to be clinicians to serve in smaller communities, and, therefore, training in practical dermatology should receive the greatest emphasis in most instances. It has been shown in the current study that formal lectures and demonstrations are insufficient for uniform attainment of proficiency. The more individualized the training, the better the results, particularly in the clinical subjects. The time has now arrived for dermatologists to be trained by means of the utilization of modern methods.

WHAT OF THE FUTURE?

Since there is no unanimity of opinion with regard to the optimum number of physicians needed in the United States, it is difficult, if not impossible, to estimate the number of dermatologists needed to provide specialist care. During and after the last war an emergency existed, and many veterans were trained in institutions with overexpanded facilities and in temporarily approved centers. Payment of tuition and a sum for maintenance, by government subsidy, has made possible the training of many additional students. Recently, two temporarily approved centers disbanded, and others may follow suit. The aim of chiefs of service should be to stress quality of training rather than quantity of graduates. If this precept is adhered to, the level of graduate teaching in some institutions will be elevated above the present standard. It may be that the number of dermatologists who can be trained adequately each year may more nearly approach 100 than the present figure of 150.

It is generally agreed that interest in and approval of teaching centers by the specialty boards have contributed singularly to the elevation of standards of practice. There would seem to be little justification for any relaxation of interest by the boards if present standards of opportunities for students are to be maintained. However, there is some basis for argument regarding the present stipulation of the American Board of Dermatology and Syphilology that all students must spend three full years of training in approved institutions before they may

take the examination. Not infrequently students lack one or two months of the required three years of training and in some instances have remained in training in order to qualify, when they could have accepted a desirable position. The capacity of students to absorb information is variable. Nevertheless, a minimum of three years of training would appear desirable in almost all cases. It would also appear that it would be unwise to permit the candidate to determine for himself the duration of training, though the doing so would save the Board a great deal of work and expense.

Selection of students for training is of the greatest importance. Perhaps more thought should be given to attracting the better students, rather than waiting for applicants to appear. It is a direct responsibility of the chiefs of service to accept students, not because of their ability to meet tuition or for other extraneous reasons, but rather because of their superior record in medical school and internship and for their intrinsic potentialities as determined by personal observation. It should be a prime duty of the chief to take a personal interest in the training of his men and later to assist them in finding locations best suited to their individual qualifications. As O'Leary emphasized, the superior candidate should have the opportunity on graduation to develop further under supervision. Students with exceptional promise should be encouraged to direct their energies toward fundamental research, and, as potential leaders in dermatology, should be given gradually increasing responsibilities in teaching and in clinic management. It is by rigorous selection and equally rigorous training that dermatology will increase its stature as an independent and important medical specialty.

ABSTRACT OF DISCUSSION

Dr. Marion B. Sulzberger, New York: We are grateful to the presenters for this most valuable guide to those who are responsible for training men in graduate courses in dermatology and syphilology. I think it will become a bible to most of us.

I should like to ask whether there is any possibility that something might be added to the Board examinations. I am certain that, in the aggregate, the goal of certification by the specialty board is an excellent influence and has assisted and will elevate the standing of the specialty. There are many men who would not study hard for three years and would not be properly trained unless the examination and the objective of certification were before them. Nevertheless, there is a small but most important group of men who should become teachers and leaders of investigation, who are not training primarily to become practitioners or to pass examinations. It would be very desirable if these men were permitted to spend a good part of their three years of training on some selected matters which Drs. Senear, Lewis and Cormia have mentioned, such as investigative work and its technics, fundamental studies in basic sciences and in fields related to the specialty, the methods of organization of departments and hospitals and teaching clinics, the pedagogic technics, the statistical technics, the sociologic aspects of cutaneous medicine and the history of cutaneous and general medicine during their period of study.

My question then is, would it be possible for a thesis in some such selected scientific field of endeavor to be made additional material which could be presented to the Board and would then receive due consideration as a part of the candidate's qualification for a certificate? Not that one wants to make two classes of dermatologists—those who are scientists and those who are not—but some of the most valuable and promising students really would prefer to be freer from the cramming and rote learning in order to engage in investigative work and more fundamental studies. Having to prepare for the Board examination takes so much of the student's time and energy in the graduate schools that it really requires a most unusual amount of strength and drive and love for science to enable a student both to prepare for the examinations and to do the collateral reading and study and actual research necessary for those who are to become leaders and teachers.

DR. GEORGE M. LEWIS, New York: The importance of certification by the Board has probably been overemphasized, although there is little doubt that there has been a progressive betterment of standards. It is indisputable that dermatologists beginning their practices are better equipped now than formerly. Perhaps the present emphasis should be mainly on selection of candidates for training who are found to have superior preliminary qualifications. It would appear that the chiefs of service of approved institutions should realize the seriousness of providing the initial facilities for training, since most students complete their training once they have started.

This paper is not an official document of the Board. It represents the views only of ourselves. It is also a pleasure to acknowledge the considerable help of Dr. C. Guy Lane, who, as former secretary of the Board, kept meticulous records which provided a source for a great deal of the data used in this paper.

The Board is rightly placed in the position of being independent and yet is extremely sensitive to the wishes of everyone connected with the specialty. On reflection, I am sure that those present here would wish it to continue to be independent. In matters of policy the Board acts as a unit, and decisions are not made by one member of the Board. The secretary would appreciate hearing from anyone regarding the Board activities and welcomes constructive criticism. It is requested that communications in regard to matters concerning the Board be addressed to the secretary and not to the individual members of the Board.

There are many schemes for training the candidates, and the Board is sympathetic to most of these. Some institutions stress training by means of didactic instruction, while others favor a more informal approach. It would seem at this time that residency training is in the ascendency. The Board does encourage training in which the student has the opportunity to carry on research during the period of his training. At the same time, there is a considerable amount of basic knowledge that must be acquired. It has been found that three years of conscientious training are required in order for the average student to become well grounded in the fundamentals of modern dermatology and syphilology.

A SURVEY OF TINEA CAPITIS, INCLUDING FAVUS

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TWENTY-SIX years have elapsed since the publication of the last report from the Massachusetts General Hospital on the incidence of tinea capitis. The only studies on this subject made at the hospital previous to the present report were presented by White,[1] in 1899, and by Greenwood,[2] in 1923.

The purpose of this paper is to report a study of 288 cases of tinea capitis, including favus. The survey covered a period of six years, beginning Jan. 1, 1941 and ending Dec. 31, 1946. During that period we observed no epidemic of tinea capitis.

The species of fungi involved and their incidence in the series are presented in table 1. The findings compare with those of Greenwood,[2] who observed Microsporum lanosum in 67.5 per cent, Microsporum audouini in 25 per cent and Trichophyton schoenleini in 7.5 per cent of cases. It may therefore be concluded that no change occurred in the relative incidence of M. lanosum and M. audouini in cases of tinea capitis recorded at the Massachusetts General Hospital in twenty-five years. White,[1] however, in a series of 279 cases of ringworm, reported M. audouini as the predominant organism; M. lanosum was not mentioned. Since White's report, which was published fifty years ago, a pronounced shift has taken place in the incidence of the different species causing tinea capitis in the same locality. Of course, it must be taken into account that the hospital draws its patients from a much larger area than formerly.

Read before the Sixty-Seventh Annual Meeting of the American Dermatological Association, Inc., Murray Bay, Quebec, Canada, June 2, 1947.

1. White, C. J.: Ringworm as It Exists in Boston, J. Cutan. Dis. **17**:1-17, 1899.

2. Greenwood, A. M.: Report on Cultures of Parasitic Fungi, Arch. Dermat. & Syph. **8**:81-82 (July) 1923.

Lewis and Hopper [3] reported the causes of tinea capitis as observed in the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, in a series of 292 cases covering a period from 1935 through the first six months of 1938. The data were: M. lanosum, 39.6 per cent; M. audouini, 39.3 per cent; Trichophyton violaceum, 7.5 per cent; T. schoenleini, 5.8 per cent; Trichophyton crateriforme, 1.7 per cent; Microsporum fulvum, 1.0 per cent; Trichophyton gypseum, 0.3 per cent, and undetermined species, 4.7 per cent. The series included an epidemic of 15 cases, all due to M. audouini. If these are omitted, the incidences of M. lanosum and M. audouini become 42.2 and 34.1 per cent, respectively. These findings indicate that except in an epidemic M. lanosum is responsible for the greater number of cases of tinea capitis in New York as well as Boston. An increase of cases due to M. audouini, however, has been observed in the last three years. In the series of Lewis and Hopper the genus Trichophyton, exclusive

TABLE 1.—*Incidence of Species of Fungi in 288 Cases of Tinea Capitis*

Species	Number of Cases	Percentage
M. lanosum (M. canis)	188	65.3
M. audouini	73	25.4
M. fulvum (M. gypseum)	2	0.7
T. schoenleini	22	7.6
T. gypseum (T. mentagrophytes)	2	0.7
T. sulfureum	1	0.3
Totals	288	100.0

of T. schoenleini, was present in 9.8 per cent of cases, as compared with 1 per cent in the present series. T. schoenleini was found in 7.6 per cent of the cases in the present series, as compared with 5.8 per cent in that of Lewis and Hopper. The higher incidence of the species in this survey is probably due to the inclusion of the two families with cases of favus in four generations of each.

In Weidman's [4] report of 36 cases in Philadelphia, it was noted that cultures from 50 per cent of patients yielded M. lanosum, 41.7 per cent M. audouini and 8.3 per cent other species.

Livingood and Pillsbury [5] reported 130 cases of ringworm of the scalp in persons from families in the lower economic stratum of central and south Philadelphia. Ninety-six per cent of the patients were

3. Lewis, G. M., and Hopper, M. E.: Introduction to Medical Mycology, Chicago, The Year Book Publishers, Inc., 1943.

4. Weidman, cited by Livingood and Pillsbury.[5]

5. Livingood, C. S., and Pillsbury, D. M.: Ringworm of Scalp: Prolonged Observation, Family Investigation, Cultural and Immunological Studies in One Hundred and Thirty Cases, J. Invest. Dermat. **4**:43-57, 1941.

Negroes. In this series, culture in 96.2 per cent of cases yielded M. audouini, 3.1 per cent M. lanosum and 0.7 per cent M. fulvum.

Benedek and Felsher [6] reported a series of 140 cases of tinea capitis in Chicago, in which the causative organisms were as follows: M. audouini, 81.5 per cent; M. lanosum, 12.2 per cent; not specified, 1.4 per cent; T. crateriforme, 1.4 per cent; Achorion schoenleini (T. schoenleini), 1.4 per cent, and Achorion gypseum (M. fulvum), 2.1 per cent. The incidence in the report is at wide variance with our findings. In our series the percentage of Negroes was negligible, whereas in the series of Livingood and Pillsbury and in that of Benedek and Felsher it was high. This may account for the difference.

TABLE 2.—*Incidence of Tinea Capitis According to Sex*

Sex	Number of Cases	Percentage
Male	165	62
Female	101	38
Totals	266	100

TABLE 3.—*Incidence of Species of Fungi According to Sex in 256 Cases*

		Species			
		M. Audouini		M. Lanosum	
Sex	Total Number of Cases	Number of Cases	Percentage	Number of Cases	Percentage
Male	156	55	75	101	55
Female	100	18	25	82	45
Totals	256	73	100	183	100

Shaw [7] in a report on tinea capitis in southeastern Tennessee, stated that from July 1942 to February 1946, 22 patients were seen. Three were Negroes and 19 white persons; 95.5 per cent of the patients were infected with M. lanosum, 0.5 per cent with the genus Trichophyton and none with M. audouini.

Sixty-two per cent of the patients with tinea capitis exclusive of favus in our series were males (table 2).

The striking predominance of M. audouini in the male sex—a ratio of 3:1 (table 3)—corresponded with the findings of other observers.[8] The incidence of M. lanosum was almost equal in both sexes.

6. Benedek, T., and Felsher, M.: Epidemiology of Tinea Capitis: I. Study of Tinea Capitis in Dispensary, Arch. Dermat. & Syph. **49**:120-123 (Feb.) 1944.

7. Shaw, C.: Tinea Capitis in Southeastern Tennesse, Arch. Dermat. & Syph. **55**:258-259 (Feb.) 1947.

8. Lewis and Hopper.[3] Livingood and Pillsbury.[5] Benedek and Felsher.[6]

As indicated in the accompanying chart the age was recorded in 257 cases. The youngest patient in the series was 6 months old and the oldest 20 years. Three were between the ages of 14 and 20. The greatest incidence of the disease was at the ages of 6 and 7. The average age was 6 years 2 months.

It is interesting to note that some of the patients with tinea capitis who were at the age of puberty showed lack of physical signs of maturity. This was exemplified in one family in which 2 brothers were affected in the following manner: tinea of the glabrous skin only was observed in the case of a boy of 11½ who showed physical signs of maturity, whereas his brother, who was 13½ but did not show signs of maturity, had tinea capitis. It may be of value to study adults with tinea capitis from the point of view of production of androgens.

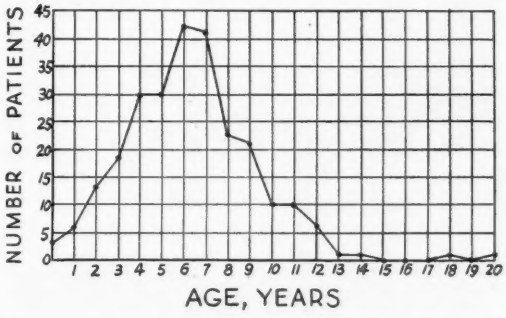

Fig. 1.—Incidence of tinea capitis according to age in 257 cases.

Of the patients in 266 cases of tinea capitis not including favus, 59 (22.2 per cent) required treatment with epilation by roentgen radiation (table 4).

TABLE 4.—*Cases in Which Roentgen Epilation Was Required*

Organism	Number of Cases	Percentage
M. lanosum	22	37.3
M. audouini	32	54.2
Trichophyton (various species)	1	1.7
Unidentified	4	6.8
Totals	59	100.0

Although the highest percentage of cases in which patients required epilation by roentgen radiation were due to M. audouini (54.2 per cent), 37.3 per cent of patients with tinea capitis caused by M. lanosum also

required this treatment. All patients with tinea capitis were treated with local therapy and manual epilation before being referred for epilation by roentgen radiation. It is therefore unwise to assume,

Fig. 2.—Favus of the scalp and glabrous skin with typical scutula in the patient in case 1.

Fig. 3.—Favus of the scalp in the mother of the patient in case 1.

once M. lanosum is cultured, that the disease will be nonresistant and will yield to local therapy alone.

The cases of favus presented were in patients whose family histories included other cases with involvement of the scalp, glabrous skin and finger nails.

REPORT OF TWO CASES

CASE 1.—P. C., a boy of 6 who had been born in Massachusetts and whose parents and grandparents had been born in Massachusetts, reported to the clinic on Jan. 6, 1944 because of loss of hair, crusting and scarring of the scalp and a

Fig. 4.—Favus of the finger nails in the grandmother of the patient in case 1.

Fig. 5.—Direct photomicrograph of a hair, showing air spaces, myceliums and large spores in chains.

rash on the face and the upper portion of the trunk. The scalp condition had been present since the age of 1, and the glabrous skin had become involved within the past year.

On further questioning, it was learned that the patient's mother had had trouble with the scalp, that his maternal grandmother had had scars on the scalp, as well

as deformed finger nails, and that his maternal great-grandfather, who had been born in Canada, had had crusting and scarring of the scalp.

Physical examination of the patient's scalp disclosed yellow-brown crusts (some pierced by hairs), scarring and loss of hair. The odor emanating from the scalp was offensive. The clinical picture was characteristic of favus. The face and the upper part of the trunk showed typical scutula (fig. 2).

Examination of the mother's scalp revealed extensive scarring, with areas showing loss of hair intermingled with yellowish crusting (fig. 3). The grandmother had burned-out favus of the scalp; the finger nails showed discoloration and deformity (fig. 4). The toe nails were uninvolved.

Results of microscopic examination and positive cultures of material taken from the affected hairs, nails and skin were characteristic of T. schoenleini (figs. 5, 6 and 7).

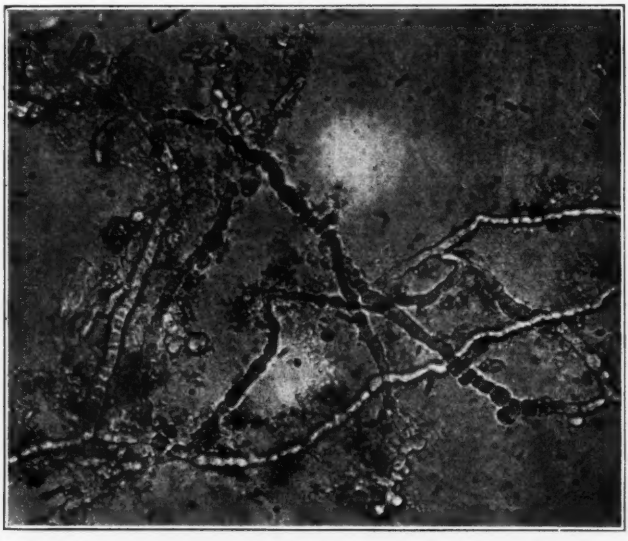

Fig. 6.—Direct photomicrograph of material from finger nails, indistinguishable from that in tinea ungium caused by organisms other than T. schoenleini.

CASE 2.—F. V.,[9] a boy of 14 born in Massachusetts, reported to the clinic on May 4, 1944 because of a scalp condition of ten years' duration. The patient's mother, who had been born in Massachusetts, as well as the maternal grandparents and great-grandparents, who had been born in Canada, had had a similar condition.

Physical examination disclosed scattered yellow-brown crusts on the scalp, but little scarring or loss of hair. A brother and a sister showed a similar picture. A 17 month old brother had a crusting and scaling patch on the vertex of the scalp.

Direct microscopic examination and cultures confirmed the clinical diagnosis of favus.

9. This patient was referred by Dr. L. A. Anderson, of Springfield, Mass.

These cases are presented because of the presence of favus in the two families for four successive generations, the presence of favus in members of one family for three successive generations born in the United States and the presence of favus involving the glabrous skin and the finger nails.

SUMMARY

A study of the incidence of species of fungi in cases of tinea capitis recorded in the dermatologic clinic of the Massachusetts General Hospital reveals that M. lanosum is responsible for the majority of cases (65.3 per cent).

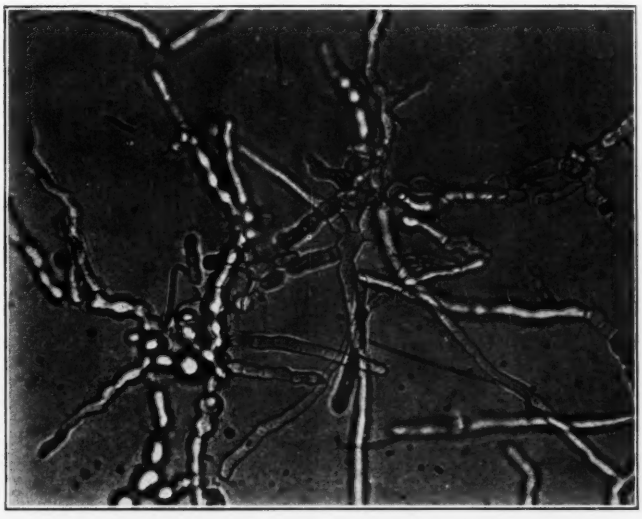

Fig. 7.—Culture mount, showing "favic chandeliers" and chlamydospores.

One and a half times as many males as females were seen with tinea capitis. M. audouini was observed three times as often in the male patients, whereas M. lanosum was observed almost equally in both sexes.

In this series, the youngest patient was 6 months and the oldest 20 years. The average age was 6 years 2 months.

It is believed that a study of production of androgens in adults with tinea capitis would offer the opportunity of valuable findings.

Treatment by roentgen epilation was resorted to in 22.2 per cent of cases, of which 54.2 per cent were caused by M. audouini and 37.3 per cent by M. lanosum (cases of favus were not included in this group). The figures confirm that tinea capitis caused by M. audouini is more resistant to treatment than the form caused by

M. lanosum, but it should be noted that in a fairly high percentage of the cases caused by M. lanosum the condition did not respond to the routine local treatment and manual epilation used in the clinic before roentgen epilation was employed.

Cases of favus in two families of four generations each are reported. In one case there was involvement of the finger nails, and in another involvement of the glabrous skin. All the patients had involvement of the scalp. In one family three generations and in the other two generations had been born in the United States.

ABSTRACT OF DISCUSSION

DR. ANDREW M. DAVIDSON, Winnipeg, Manitoba, Canada: In the series of cases of tinea capitis including favus in the city of Winnipeg, the frequency of M. audouini was three times as great as that of M. lanosum, but the series covered the period of an epidemic due to M. audouini.

This epidemic was cleared up eleven years ago; another case due to M. audouini was not reported until last year, when 3 children, one of school age, in a family which had moved from Calgary, Alberta, were all found to be infected with M. audouini.

The incidence of cases of tinea capitis caused by M. lanosum has remained at about the same level, but this type has come mostly from the country areas. Those cases due to T. gypseum, T. violaceum or Trichophyton album (T. schoenleini) are much less frequent; this type also comes from the surrounding farming country, usually in the form of kerion.

I have been especially interested in tinea capitis of the human type in the city schools and orphanages. During the epidemic from 1932 to 1936, the problem was successfully tackled with the support of the city medical officer of health.

Ringworm of the scalp was made a notifiable disease, and infected children were excluded from school. All patients were treated in the department of dermatology of the Children's Hospital in Winnipeg. The school nurses were supplied with inexpensive, homemade portable lamps with filters of Wood's glass. In every school where disease of the scalp was discovered, all children filed through an emergency darkroom, where they were examined with Wood's lamp.

Those infected with ringworm were isolated; the diagnosis was later verified in the Children's Hospital, where a water-cooled quartz lamp was installed for this purpose. Children in the orphanages were similarly examined.

A competent mycologist from England made a study of the cultures on French proof agar. The first cultures were verified by Dr. Howard Fox and Dr. Muskatblit of New York. Samples were then sent to the Central Bureau, in Holland, and the Manitoba type cultures were registered. Later in the investigation, all cultures were verified by the hyphal fusion method described by Professor Buller. This method was applicable to the dermatophytes, as to other fungi. Myceliums from similar species show hyphal fusions; those from different species do not.

The children infected with M. audouini were treated by roentgen epilation.

Dr. Swartz stated that in 37.3 per cent of the cases in his series due to M. lanosum the condition did not respond to local treatment.

There were no resistant cases in the series in Winnipeg after adoption of the plan of hospitalizing all patients with ringworm of the scalp; this was probably due to more thorough treatment than had been carried out in the patients' homes.

The most important part of the treatment was the continued use of Wood's lamp for the detection and removal of all infected hairs. Because of this, no child returned to school until the cure was complete.

Physicians in Winnipeg have been fearful of another epidemic of M. audouini, and my colleagues have been on the watch for any immigrants with ringworm. There have been epidemics in Vancouver, British Columbia; Calgary, Alberta; Ottawa, Ontario, and Minneapolis.

Our experience may be summarized as follows: Ringworm and favus should be notifiable diseases under the control of a public health authority; careful studies of cultures of the fungi are essential for correct diagnosis; infected persons should be isolated until cure is proved with Wood's lamp; epilation should be the responsibility of a dermatologist experienced in this work; the establishment of a department to eradicate ringworm in school children, which includes persuasion of the powers that be, is a task of the first magnitude.

DR. JAMES HERBERT MITCHELL, Chicago: For the December 1946 meeting of the American Academy of Dermatology and Syphilology I attempted to make a survey of tinea capitis on the entire North American continent. With a few exceptions my sources of information were private.

The declining epidemic of ringworm originated in New York city. I was unable to get any cooperation from health departments, but individual physicians later sent me various figures, which show that the epidemic traveled straight across the country.

Dr. Swartz has stated that there were no signs of the epidemic in Boston. Drs. Pillsbury and Livingood said the same as regards Philadelphia. However, in crossing the country, the epidemic hit Syracuse, Rochester and Buffalo in New York state and Ann Arbor and Flint in Michigan, and in Chicago it became a real menace. Probably 6,000 or 7,000 cases have been recorded in Chicago.

The original survey of the schools in Chicago indicated that 2.6 per cent of all public school children examined were infected. The survey for the first five months of 1947 indicated that infection was present in only 0.6 per cent of more than 200,000 children who were examined by the health department. I was unable to get any figures on the cases reported by Chicago physicians to the health department, which does not seem to be able to cope with the situation.

The epidemic was mild in Eastern Canada and did not extend to Western Canada. It went south more or less directly.

In my experience, the causative agent in this epidemic has almost invariably been M. audouini. I have found only 1 instance of T. violaceum and 1 of M. lanosum; material from the latter was sent to me from Springfield, Ill., for culture.

It is interesting to note that the Southeastern states were more or less spared except for the northern part of Virginia and in Richmond. I do not know why. The epidemic was severe in the Twin Cities, but it was not much of a problem in Kansas City, Mo. It gradually died out while going westward and ceased to be a problem on the West Coast.

Dr. Davidson has stressed the importance of making ringworm of the scalp a reportable disease. In Anderson, Ind., a town of 42,000, there were 432 cases at the peak. The commissioner of health, Dr. E. M. Conrad, has carried on a most energetic campaign to stamp out the disease. He has just reported to me that in the first five months of this year there have been no new cases.

Dr. Moore made the statement in 1941 that he knew of only 4 cases of infection with M. audouini in St. Louis. He estimates, at the time of this report, that there are at least 4,000 cases due to M. audouini in St. Louis.

Dr. Oliver told me that he was getting good results with local treatment and was abandoning the use of roentgen epilation. Improved results with local treatment may be due in part to better care of children since the war and to the fact that the epidemic is undoubtedly dying out. My experience indicates that the infection was not spread at barber shops but was carried on seats in public conveyances and motion picture theaters. Most of the children infected were small, and their heads would have rested against the backs of the seats.

Infection was seven times more common in boys than in girls. Some of the girls I saw with the infection parted their hair in the middle and had pigtails, offering ideal surfaces for contact.

I have not had much success with local treatments. I have tried them all from time to time and have finally resorted to epilation, which in my experience has been the most satisfactory method of treatment. I have not tried treatment with androgens, but I believe Dr. Rattner has had considerable experience with such methods.

I should like to show slides of a series of cultures, illustrating a crude method of evaluation of various fungicides. [Slide] The first view illustrates the control. All the cultures were made with hairs from the same lesion of the scalp. The second culture was made with a soap, supposed to be effective. The next was made with a mixture of equal parts of phenol and camphor, an inert preparation except when water comes in contact with it and thereby liberates the phenol. The fourth was made with a similar mixture of phenol and camphor, to which water has been added, and the next with benzalkonium chloride U.S.P. (zephiran chloride®). The next two cultures were made with sopronol ointment® (a water-soluble ointment containing sodium propionate 12.3 per cent, propionic acid 2.7 per cent, sodium caprylate 10 per cent, zinc caprylate 5 per cent and dioctyl sodium sulfosuccinate 0.1 per cent). The last was made with phenyl mercuric salicylate, a preparation which kills everything within reach but is extremely irritating. I have used it with a 1 per cent solution of acetone in infected scalps with some benefit.

[Slide] Here is the much advertised zincundecate (desenex®). The hairs were embedded in the ointment. No attempt was made to clean the ointment off the hairs; they were merely planted on a surface of French proof agar. M. audouini seemed to grow a little better with desenex® than without.

[Slide] The next views are of cultures made from scales after treating a patient's foot, which I shall show you next. The foot was treated for two weeks with desenex® without clinical improvement, and positive cultures could still be obtained from the tops of the vesicles. I have failed in years gone by to get positive cultures after treatment with ointment of benzoic and salicylic acid N.F. (Whitfield's ointment), and I have long since discontinued routine culture after this treatment.

[Slide] One serious complication occurred in the roentgen epilation: The development of alopecia areata. This was not due to errors in technic or use of the x-ray apparatus. With the five point method the alopecia would have been at one of the five points, but in this case it was in the lower left part of the occipital area, which could not possibly have been overtreated with careful technic.

Epilation in this case was done not in my office but at the Presbyterian Hospital, in January 1946. When I first saw the patient I was alarmed, but the family was cooperative. I saw the patient a year later, after all the hair had grown in, and no further difficulty has developed at the time of this report.

DR. EDWARD A. OLIVER, Chicago: As Dr. Mitchell has said, the prevailing organism in Chicago has been M. audouini.

Roentgen epilation is not always wanted by the parents of patients and is difficult to use in the smaller communities when expert technicians are not at hand. Dr. Felsher, of Northwestern University, has just completed a study of 150 cases caused by M. audouini in white children. He used the ointment originally suggested by Dr. Schwartz.

Dr. Felsher effected a cure in 105 cases in the group. The shortest period required for cure was three months and the longest fourteen months; the average was six and a half months. Eight patients, whose infection was limited to one fourth of the scalp, were cured in an average of five and a half months. Of the patients with severe cases only 25 per cent recovered fully, in an average period of eight and a half months.

Of the 45 patients not cured, the infections in 7 showed an improvement of less than 50 per cent. Of the 38 patients whose infections improved over 50 per cent, improvement of 75 per cent was noted in 14. The severity of the disease, as manifested by the size and number of the lesions, was an important factor in determining the rate of recovery. The duration of the disease before treatment was begun and the age of the patients had but little bearing on the time required for the cure.

Unfavorable reactions to the ointment were not observed; it has proved superior to other topical applications. They were all tried, including the use of androgens. In the mild and moderately severe cases, this ointment gave results that compared well with those obtained by roentgen epilation. However, roentgen epilation was superior in the very severe cases.

DR. C. GUY LANE, Boston: Some years ago I reviewed, with regard to the time of the children's return to school, a series of cases of tinea in which the patients were treated with roentgen radiation. (The study was never published.) During a period of four years, some 112 patients were treated with roentgen radiation. Forty of these children were able to return to school in the fourth week, 37 in the fifth week and 35 in the sixth week.

At the time when these children returned to school, they were not all checked with Wood's lamp and with cultures, but results of microscopic examinations were negative and the children apparently were clinically free of the disease.

Around Boston there is considerable difference in the various communities with regard to permission for children to return to school. Sometimes the matter is in the hands of the school physician and sometimes in those of the school nurses, and the decision depends on their interpretation of the rules of the board of health in the particular community.

There ought to be a wider publication of reliable information with regard to the infectivity of ringworm and the conditions under which children may return to school. I hope there will be wider publication of the report of the committee which studied the matter in New York under the chairmanship of Dr. Lewis.

With regard to the photograph which Dr. Mitchell showed, since 1939 there have not, as far as I know, been any cases of permanent alopecia caused by roentgen radiation in Boston. I have seen 4 patients with permanent alopecia; in 2 of these cases, as I recall, epilation was performed in Europe before the patient came to this country.

DR. MAURICE SULLIVAN, Baltimore: I shall confine my comment to sterilization of instruments used in barber shops. In Baltimore, conformance with

the regulations is supervised by a board of examiners, barbers themselves and elected by the barbers. Therefore, the health department finds itself in the position of being assured by the barbers that regulations regarding sterilization are enforced. Such assurances are inconsistent with the facts; a trip to any tonsorial establishment dispels the idea of sterilization in practice. There is not the slightest attempt at sterilization. Barbers would be anxious to sterilize their instruments if they thought it important, but they will not engage in methods of sterilization which are time consuming and which interfere with their livelihood. Many barbers disapprove of the method recommended by the United States Public Health Service, as there are objections to immersing clippers in oil. Sterilization by vaporization is impractical. Therefore, when one approaches a group of barbers and asks, "What type of sterilization would you consent to adopt?" they reply that they would like a method which is brief and effective, by which sterilization could be accomplished within half a minute.

With this request in mind, I consulted an inventor and an engineer and requested that they design an instrument which would blow a blast of hot air onto a pair of clippers and thoroughly clean the instrument. (Preliminary tests in our tinea capitis clinic indicate that it is possible to sterilize instruments with brief blasts of dry heat at high temperatures.) The first model was large and unwieldy. A second, smaller model is now being made. When it is completed, I hope to present to the barbers a small sterilizer, which requires only the insertion of a pair of clippers and the turning of a switch; a blast of hot air will then blow all the hairs from the clippers and suck them down into a collecting compartment.

Dr. Mamnett A. Dixon, Toronto, Canada: In Toronto, at the Hospital for Sick Children, cultures have been made with material from patients with ringworm of the scalp. Fifty per cent of the cultures, from 36 patients to date, have shown M. audouini and 50 per cent have shown M. lanosum.

Dr. John G. Downing, Boston: I believe that if Dr. Swartz were to compute yearly incidence he would find that in the past few years there has been a change in the fungus primarily responsible for this disease. Mycologic studies, made in the laboratory of the Boston City Hospital during the eighteen month period from Nov. 1, 1945 to May 1, 1947, indicate that the incidence of various fungi in 115 positive cultures was as follows: M. audouini, 68 (approximately 60 per cent); M. lanosum, 44 (38 per cent), and T. schoenleini, 3 (2 per cent). Of these 115 patients, only 6 were girls; 5 of the girls were Negroes. The girls' lesions had first appeared in the bald areas left by tight braiding. The average age of all patients at onset of the disease was 6½.

Forty-six cases were followed for a sufficient length of time to evaluate treatment and prognosis. Clinical cure was determined after negative results in 3 weekly fluorescence tests, plus negative cultures. Tinea capitis due to M. lanosum, regardless of the type of treatment, was pronounced cured on an average in less than three months. Eighteen per cent of the infections due to M. audouini were cured by local treatment alone, without roentgen radiation. Thymol in chloroform was used in 3 cases due to M. audouini; 2 patients were pronounced cured. If these 2 cases had not been considered, the number would have been near 10 per cent, the figure for spontaneous cures reported by Dr. Lewis. Of the 3 patients with favus, 2 were mother and son in one of the families in Dr. Swartz's report; these 2 had had the disease for years. The third patient was a friend of the son, who had been afflicted for one year and showed a single patch. In 1944, Morris reported a cure in 2 cases of infection due to T. schoenleini in which a 10 per cent solution of thymol in chloroform was used (*New England J. Med.* **230**:667-669 [June 1] 1944.) The patients are well at the time of this report.

DR. GEORGE M. LEWIS, New York: The present epidemic of tinea capitis presents to public health authorities a challenge which many have not seen fit to accept seriously. Compared with other infectious diseases ringworm of the scalp, while not a menace to life, still commands respect because of its contribution to misery and because of the coincident economic loss. There are many divergent views on different phases of its control, its insidious spread over the country being sufficient testimony to the ineptness, the lack of knowledge and, often, the lack of interest of many of our public health officials. The hope that dermatologists will improve the therapy and that natural forces will operate sufficiently well for the disease to become less prominent would appear to be that of many city, state and federal public health workers who would hardly dare to be so casual about any other infectious disease.

It would now seem that the local therapy advocated by Swartz and his co-workers may be slightly more effective than remedies which have been used previously and that, if persisted in for four months or more, it will effect a cure in a considerable proportion of cases. While it is not to be considered as a specific, it does indicate that a chemotherapeutic remedy may eventually be found to control this infection satisfactorily.

DR. SAMUEL AYRES JR., Los Angeles: The question of alopecia has been mentioned. I have under my care a patient who was treated not for ringworm but for an epithelioma of the forehead, with 1800 r. There was complete protection of all surrounding tissues.

Within approximately two weeks, a typical patch of alopecia, with exclamation point hairs, developed behind the treated area.

DR. JACOB H. SWARTZ: I want to mention that I am not the Dr. Schwartz whom Dr. Oliver mentioned in connection with the course of treatment.

I, too, want to stress the differences noticed lately in the cultures of M. lanosum. They are more difficult to identify on gross examination. On culture mounts, the typical spindle-shaped fuseaux may be seen only in the old cultures.

Our experience, unlike that of Dr. Lewis, has been that the response to treatment has been poorer.

We have completely stopped using thallium acetate because of the ill effects.

To answer Dr. Downing's report and suggestion, I have broken down my figures for the last three years and I have them here: In spite of the fact that the percentage of cases due to M. audouini has increased in the past three years, in 1944 there was still a predominance of M. lanosum (44.2 per cent) over M. audouini (36.2 per cent). In 1945 the percentages were: M. lanosum, 46.9, and M. audouini, 41.1. In 1946 the trend had changed, and the percentages were: M. lanosum, 53, and M. audouini, 34. Therefore, even though the relative incidence of M. audouini has increased, there is still a predominance of M. lanosum in our series.

HYPERTROPHIC DARIER'S DISEASE AND NEVUS SYRINGOCYSTADENOMATOSUS PAPILLIFERUS

Histopathologic Study

HERMAN BEERMAN, M.D.
PHILADELPHIA

TWO RECENT events emphasize the desirability of resurveying certain of the histologic appearances of Darier's disease (keratosis follicularis). The first is the recognition of familial benign chronic pemphigus and its separation from the concept of Darier's disease (by Hailey and Hailey, and others). The other is the following experience involving a number of competent pathologists, both dermatologic and general. In the course in pathology given by Weidman at the American Academy of Dermatology and Syphilology in Chicago in 1940, an "unknown" slide (3675) was included among those of the tumors as an example of Darier's disease, with pseudoepitheliomatous hyperplasia. When this slide was presented to the round table on pathology at the same meeting, those present stated the belief that the specimen represented nevus syringocystadenomatosus papilliferus. Since then, the specimen has gone the rounds, and considered diagnoses have varied from atypical squamous cell epithelioma, to a combination diagnosis, such as, "At one edge of the section there were changes suggestive of Darier's disease; in the middle, there were changes that looked very much like adenoma hidradenoides (Perthes) as depicted in Gans's Histology of Diseases of the Skin,' volume 2, page 279; in places, this type of change went over to frank basal-squamous cell epithelioma." It is my purpose, therefore, to review briefly the basic histologic features of Darier's disease; to demonstrate that pseudoepitheliomatous hyperplasia of basal cells is an essential feature of this disease, especially in the papillomatous form, and to establish criteria for the histologic differentiation of this unusual variety of Darier's disease from a nevus of the sweat apparatus.

VEGETATING DARIER'S DISEASE: REPORT OF CASES

In addition to the specimen from the case (slide 3675) presented by Weidman, as noted previously, my associates and I have studied for the past seven years another extreme example of the vegetating

Read at the Sixty-Seventh Annual Meeting of the American Dermatological Association, Inc., Murray Bay, Quebec, Canada, June 2, 1947.

From the Department of Dermatology and Syphilology, University of Pennsylvania School of Medicine, Donald M. Pillsbury, M.D., professor.

type of Darier's disease. Observations of these cases and material from a case of nevus syringocystadenomatosus papilliferus form the basis for this report.

CASE 1.—The patient was a 40 year old nonleprous Negro at the United States Marine Hospital, Carville, La. The late Dr. Ralph Hopkins made the diagnosis of Darier's disease. Through the courtesy of Dr. Sam Black and Dr. H. E. Hasseltine, Dr. Weidman received a specimen from the perianal region,

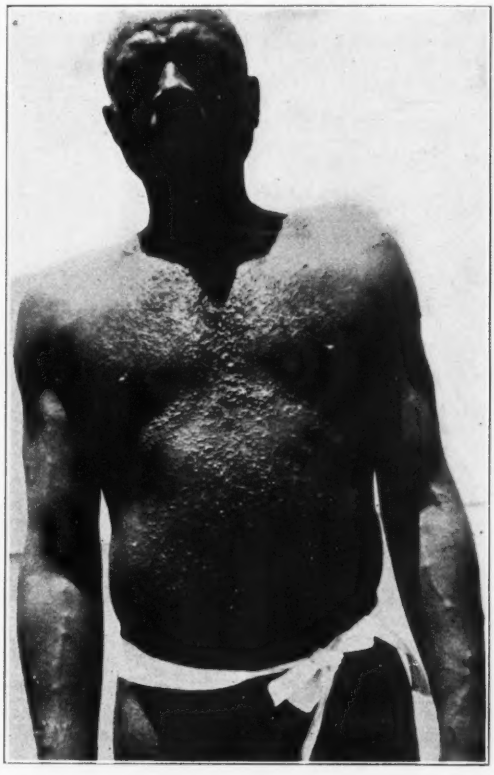

Fig. 1 (case 1).—A front view, showing the more or less usual papular form of Darier's disease in seborrheic distribution.

as well as clinical photographs (figs. 1 and 2). The process, nonpruritic, had been present for twenty years. The essentials of Dr. Weidman's microscopic description of the specimen are submitted as follows (fig. 3): "The diagnosis of Darier's disease could have been made only with qualifications were it not for the presence of one or two very small lesions of Darier's disease at the extreme end of the section and on the surface. In this location the typical lacunas and fairly good examples of psorosperms were observed. Toward the

center of the section, the general principles in the construction of a lesion of Darier's disease could be identified, but they had developed on a gigantic scale. For example, hyperkeratotic villosities projected on the surface, and between them, at their bases, the lacunas could be identified. It was at this point that a puzzling picture obtruded in the form of a pseudoepitheliomatous hyperplasia proceeding from the floor of the lacunas.

"The pseudoepitheliomatous hyperplasia ranged from small to huge infiltrations. Mitotic figures were abundant. At times small pearly bodies appeared. Occasionally a psorosperm could be identified, and at one place foreign body giant cells were disposed around scraps of keratinous material. Most interestingly, empty clefts appeared rather consistently within this pseudoepitheliomatous material, thus indicating the preservation of the tendency to repeat the architecture (papillary) which so commonly appeared at the base of the lacunas at the surface.

Fig. 2 (case 1).—A close-up view of vegetating lesions in the anal cleft and perineum.

Indeed, it was this feature, rather than the more usually emphasized psorosperms, which identified the changes here as those of Darier's disease. Much of the pseudoepitheliomatous tissue lay below the level of the sweat glands and even attained the deep arterial plexus.

"This was a most unusual expression of Darier's disease because the psorosperms were so inconspicuous, in spite of the highly developed stage of the lesion. Indeed, the diagnosis was prompted more by the formation of lacunas, albeit atypical. There was a tremendously exaggerated hyperplasia of the tissue which ordinarily comprises the floor of the lacunas, resulting in its extension of the tissue to the deepest parts of the corium. Thereupon the question of whether or not a true cancerous change had taken place had to be met.

"I was extremely loath to make a diagnosis of cancer in any case of Darier's disease, in view of clinical knowledge. I felt thus especially when I considered what was known of the range of the possibilities of pseudoepitheliomatous hyper-

plasia. In this dilemma I had to concede that I had never seen the latter extend to such a deep position in the skin. I could understand the presence of the pearly bodies and the mitotic figures.

"All things considered, I decided against the diagnosis of cancer and should explain the deep position of the infiltration on the basis of the great mass of epithelial material which comprised the bulk of the lesion. The final answer must rest in the clinical course, pending which I should prefer to regard the changes

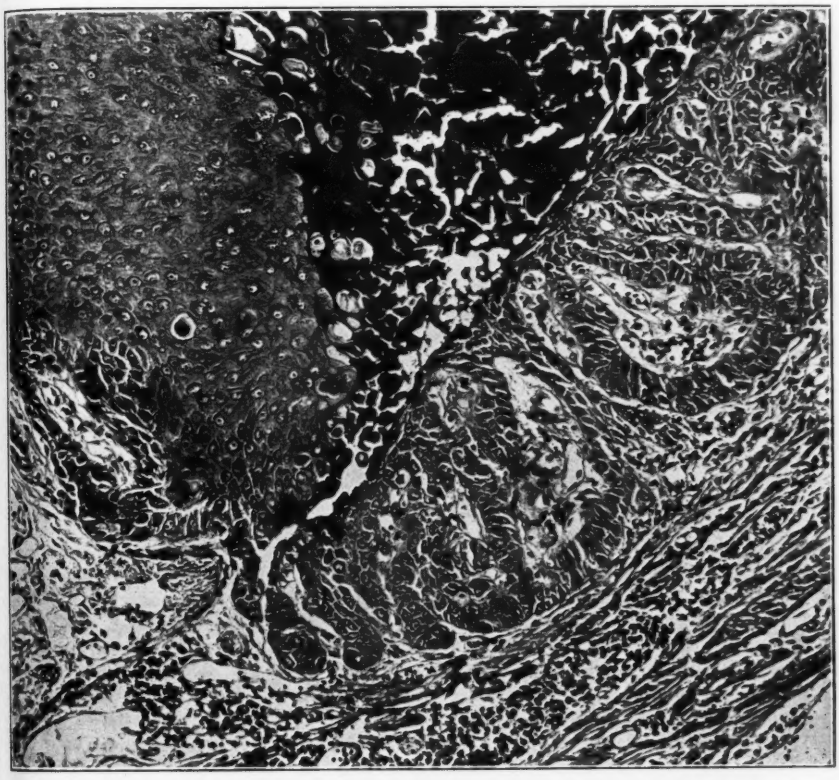

Fig. 3 (case 1).—The histologic features of hypertrophic Darier's disease: hyperkeratosis, corps ronds, grains, lacuna, acanthosis and, especially, basal cell proliferation. Mitotic figures and a scanty inflammatory reaction in the corium may be noted (slide 3675).

as those of pseudoepitheliomatous hyperplasia rather than of the cancer which the condition appears to be."

CASE 2.—The case of M. G., a white coal miner aged 43, was presented to the Philadelphia Dermatological Society in 1939 by Johnson [1] as an example of Darier's

1. Johnson, H. M.: Darier's Disease, with Possible Nevoid Changes on the Forehead, Arch. Dermat. & Syph. **41**:448 (Feb.) 1940.

disease with possible nevoid changes on the forehead. At the time of the patient's admission to the Hospital of the University of Pennsylvania, in 1939, the process had been present for seventeen years, having begun in 1922 as a "boil" on the perineum. This had ulcerated and drained for several years. In 1932 lesions had begun to appear on the sacral region. These gradually had increased in size, and new lesions had appeared higher on the back. Several years later the thorax had become affected, and in 1934 pustules had appeared on the sides of the nose. The forehead had become involved in 1937, the retroauricular region in 1938 and the scalp, pubic region and axillas in about 1940. Previous treatments of various types had had no restraining effect on the lesions. Proliferative lesions, previously removed, had recurred within several years. The status of the patient's parents is unknown, but a brother is similarly affected. A sister and 3 children are normal.

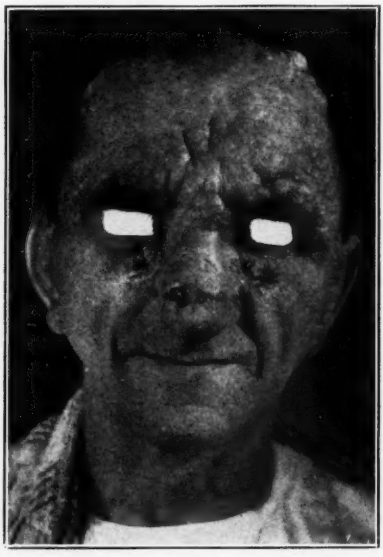

Fig. 4 (case 2).—A view showing lesions of the vegetative type on the face and scalp.

The patient was admitted to the hospital on three occasions, in 1939, 1942 and 1946. During these admissions numerous studies were made. There was no evidence of vitamin A deficiency, according to clinical examination and blood levels, nor was there any response to the oral administration of vitamin A, in a dosage of 250,000 units daily for a month. Visceral examination revealed possible hypertrophic gastritis. There was no response to roentgen therapy given to the pubic region in 1946, and surgical excision of some of the lesions of the ear and nose was done.

The lesions occurred in a somewhat seborrheic distribution (figs. 4 and 5); that is, on the scalp, the frontal, temporal and malar regions, the nose, ears and adjacent areas and the neck; in two deep V's extending over the sternum and on the abdomen anteriorly; between the scapulas and onto the lumbar region posteriorly:

in the axillas and the groins; over the pubis and in the gluteal cleft, and on the extensor, hairy surfaces of the forearms and the dorsa of the hands. The palms had a diffuse, yellowish thickening, and the finger nails were spoon shaped. Uninvolved portions of the skin were the bearded part of the face; the arms, thighs, legs and feet; the flanks and buttocks, and the external genitalia. In 1941 the oral and rectal mucosae were normal, but in 1946 there were whitish plaques on the anterior pillars and tonsillar areas. The rest of the oral mucosa was pale.

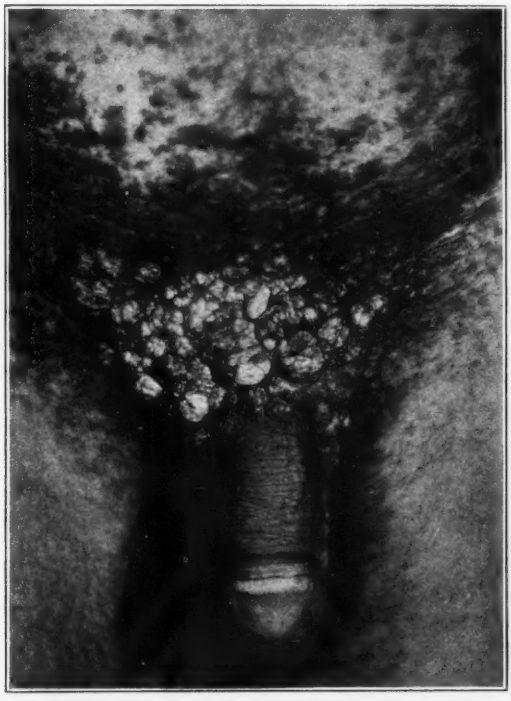

Fig. 5 (case 2).—Extreme hypertrophic lesions on the suprapubic region.

An individual early lesion was a small, firm, discrete, rose or violaceous process at or near a pilosebaceous orifice. Older lesions were larger, more elevated and purple, bronze or brown, and groups of them coalesced. The surfaces looked waxy and displayed widened orifices, from many of which a long "worm" of thickened sebum might be expressed. On the scalp, in the gluteal cleft and the groins and over the pubis, this piling up of tissue had caused the formation of tumor-like masses, punctuated with numerous gaping, glandlike orifices and deep clefts, from which the decomposed sebum and sweat gave forth a pungent odor. The masses were so situated on the face that the patient had a leonine appearance, and their deep color caused a dusky hue.

Specimens for biopsy were removed from the supraorbital region, right cheek, right bregma, ear and postauricular region, nose, hands, anal region and groin of this patient. The pathologic changes varied from a very simple picture of Darier's disease, as exemplified by the lesion removed from the hand, to extremely complicated structures, as exemplified by the lesion removed from the supraorbital region.

Fig. 6 (case 2).—Section of a lesion from the hands, showing the usual features of a papular lesion: "follicular" location, hyperkeratosis, corps ronds, acanthosis, lacunas and a slight tendency to basal cell proliferation (slide 952).

Section 952, removed from the hand, showed a verrucous surface with extensive hyperkeratosis, especially in epithelial invagination. The granular layer was normal. There were epidermal edema and moderate acanthosis. The pigment in the basal layer was preserved, especially in the less acanthotic portions of the

epidermis. Corresponding to the sites of greatest hyperkeratosis, there was basal cell proliferation. At one site (fig. 6) was a typical lesion of Darier's disease (perifollicular) with hyperkeratosis, corps ronds, lacunas and slight basal cell proliferation. There was slight round cell infiltration of the corium, and the appendages (sweat apparatus) were normal.

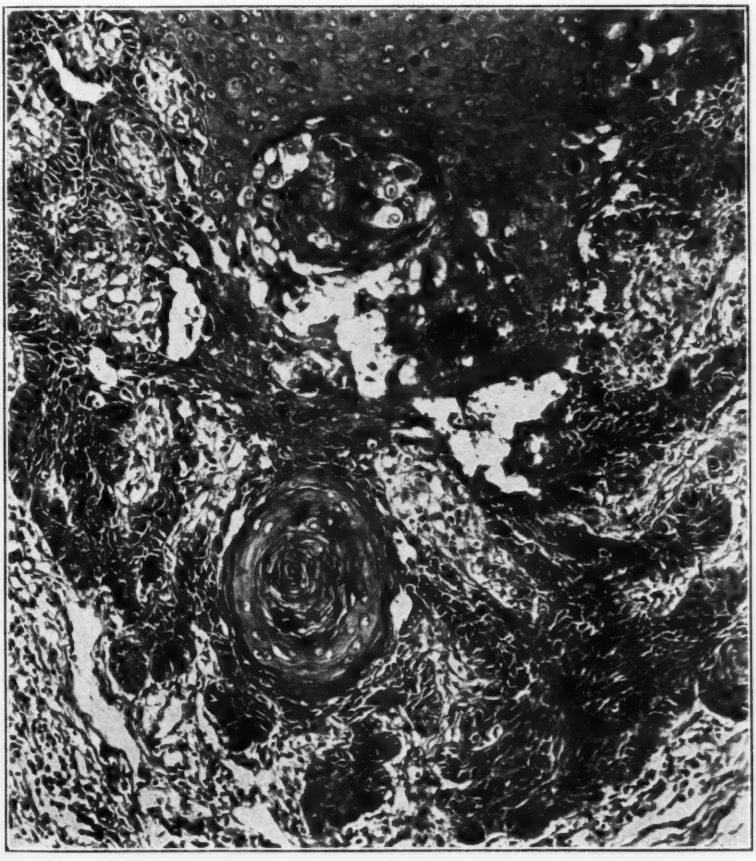

Fig. 7 (case 2).—Section of a lesion from the supraorbital region. In addition to the features of Darier's disease (hyperkeratosis, corps ronds and lacunas) there are distinct basal cell proliferations and pseudopearls (slide 946).

Section 946 was taken from the supraorbital region. The specimen had a definitely irregular surface, pronounced cauliflowerlike hyperkeratosis, frequent keratotic follicles and a profusion of corps ronds and grains. There were deep fissures, some of which extended the whole width of a rather deep section. These fissures were lined with keratin. The same features were present throughout the

entire section. There were a number of cornified cysts in the corium. (Kreibich [2]). There was marked basal cell proliferation, showing mitotic figures, with lacunas above them. In some sites this proliferation was extreme, as shown in figure 7. There were some chromatophores, a dense infiltration containing plasma cells and a number of dilated blood vessels in the corium. There were abundant hairs in the specimen.

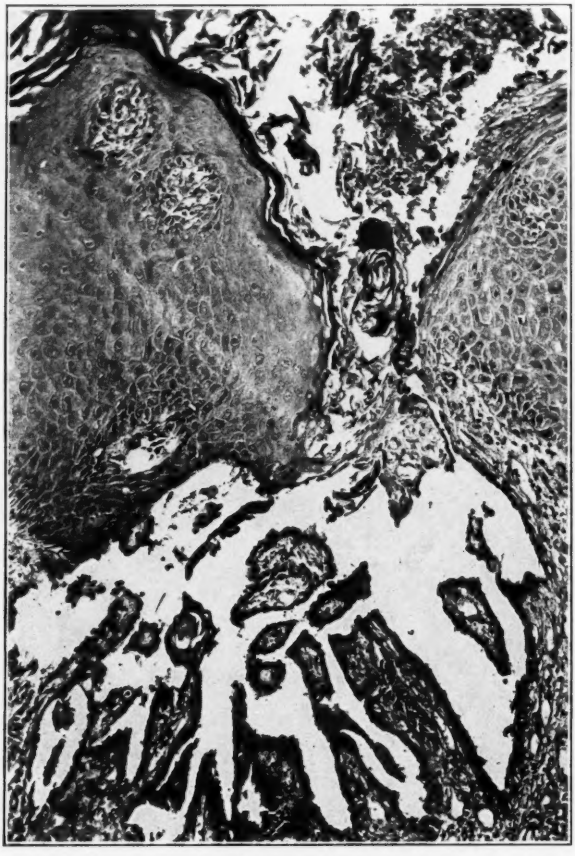

Fig. 8 (case 2).—A section from the perianal region. Note the general structure, which resembles the histologic features of nevus syringocystadenomatosus papilliferus (slide 943; × 16).

Section 943, removed from the perianal region, showed a verrucous surface, extensive acanthosis and epidermal edema. At one end of the section were

2. Kreibich: Hyperkeratose (Kyrle) und Dyskeratose (Darier), Arch. f. Dermat. u. Syph. **163**:215, 1931.

pronounced basal cell proliferation and a deep crypt (large lacuna) plugged with a crust of hyperkeratotic material and corps ronds and papilliferous projections pointed into the interior. The projections were covered by a single layer, or sometimes several layers, of flat to cuboidal epithelial cells. There was some pigment in chromatophores in the projections. Beneath this structure occurred sweat ducts such as are seen in nevus syringocystadenomatosus papilliferus. The corium con-

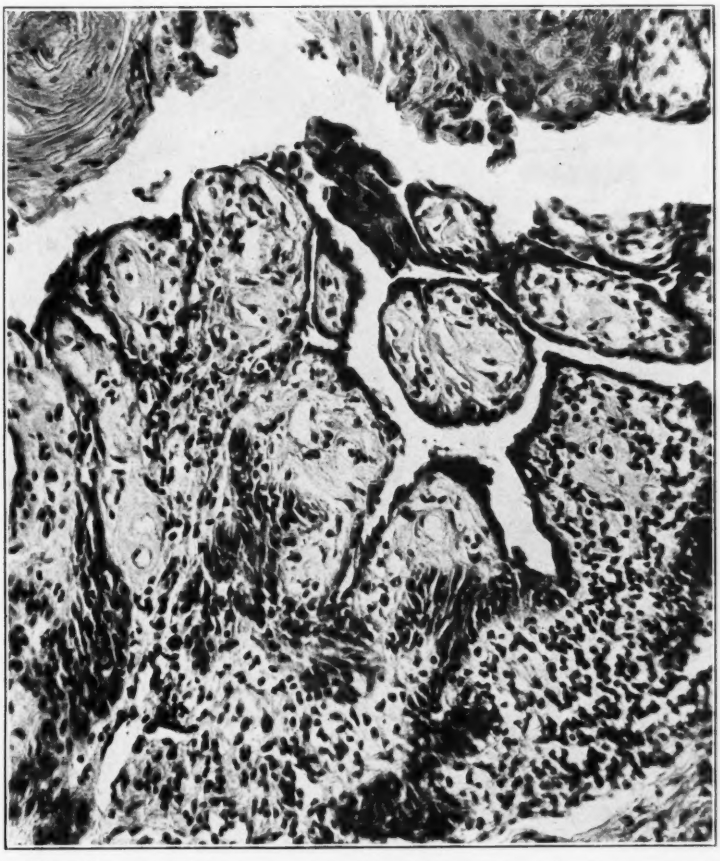

Fig. 9 (case 2).—Higher power view of the "intracystic" proliferations. Note the single layer of basal cells on the projections (slide 943; × 235).

tained leukocytes, lymphocytes, plasma cells and numerous chromatophores. There were dilated blood vessels. Typical features of Darier's disease (lacunas, hyperkeratosis, corps ronds, pseudoepitheliomatous basal cell hyperplasia, and pseudopearls) were to be seen at the other edge of the section (figs. 8 and 9).

Section 1557, removed from the right cheek, showed essentially the same features as did section 946. Conspicuous basal cell proliferation could be noted.

Section 1988, removed from the groin, also had features similar to those of section 946. Metaplasia of the prickle cells (fig. 10) lay side by side with proliferation of basal cells.

Section 2689, removed from the right postauricular region, presented a picture similar to that of section 946, but there were lobules suggestive of glandular

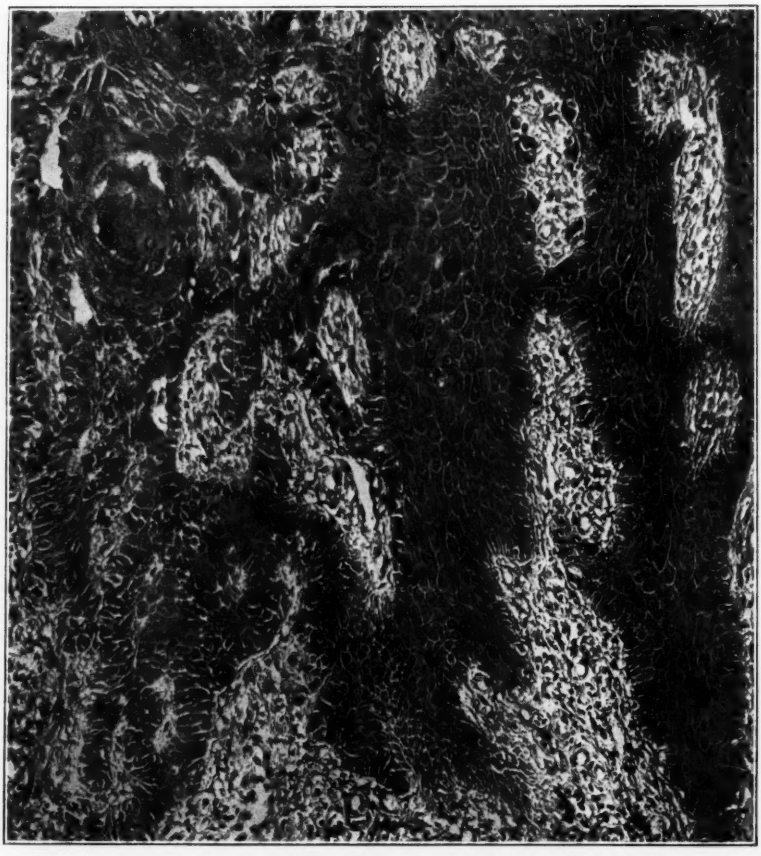

Fig. 10 (case 2).—Specimen from the groin, showing considerable hyperplasia (metaplasia) of prickle cells and basal cells (slide 1988).

carcinoma. At high levels all the basal cell "acini" had surrounding lacunas. These were really representative of cross sections of villous projections.

Section 54631 showed histologic features similar to those of section 946. Exquisite corps ronds were to be noted.

Sections 1559 and 2716 also showed changes essentially like those of section 946.

HYPERTROPHIC DARIER'S DISEASE

Clinical Characteristics.—The essential papillomatous character of hypertrophic Darier's disease, from the clinical standpoint at least, is suggested by some of the names proposed for the process, as they were collected by Brünauer[3]: *acné concréte hypertrophique* (Hallopeau), *acné cornée végétante* (Gaucher), keratosis vegetans (Crocker), *séborrhéide végétante* (Hallopeau and Fouquet), epitheliomatosis milliaris (Nékám) and *papillomatose dyskératosique* (Nicolau). Although Darier[4] later (1931) concluded that the first two points of his designation for the disease were unjustifiable, he did not deny the appropriateness of the third (*végétante*).

In Darier's disease there may be a variety of types of lesions, the sort depending on the site involved. The process usually has a tendency to the seborrheic distribution, with a special predilection for loci of intense perspiration. These include the scalp, temples, face (cheeks and nasolabial folds), retroauricular regions, neck and axillas; the presternal, interscapular, umbilical and genitocrural regions, and the mons veneris, back, gluteal regions, legs, dorsa of the feet, soles, dorsa of the hands and palms. Verruca plana may occur on the dorsa of the hands (Darier[4]). The vegetative form involves the intertriginous regions, the axillas, the inguinal and anogenital regions and, less often, the postauricular areas. Hidaka[5] found that among 70 patients with Darier's disease, the axillas and inguinal region were affected 13 times each, the genitocrural region 8 times and the anal region 6 times. In these sites, by confluence of individual lesions, the macerating effects of intertriginous surfaces and secondary infection contribute to the unusually large size of the lesions, as well as to the characteristic foul odor, matting and crusting. Clinically, the lesions, which are reddish yellow, may be plaquelike, fungating, condylomatous, papillomatous, cockscomb-like or tumorous, and sometimes there are deep fissures. Some of the lesions, umbilicated papules, may not exceed the size of a pea and morphologically resemble those of molluscum contagiosum. The crater, occasionally completely empty, is usually occluded by a gray or yellow sebaceous material. The size and odor of the lesions contribute greatly to the patients' depressed mental attitude toward this disease.

3. Brünauer, S. R., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2.

4. Darier, J., in the Proceedings of the Eighth International Congress of Dermatology, Copenhagen, Engelsen and Schrøder, 1931.

5. Hidaka, S.: Studier über die Dariershe Dermatose, Acta Dermat. **3**:191 and 373, 1924; **4**:1, 1924; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **17**:873, 874 and 875, 1925.

Histopathologic Characteristics.—Histologically, Darier's disease is essentially an epithelial process. Outstanding features are peculiar cell degenerations (dyskeratosis, the so-called corps ronds and grains), hyperkeratosis and parakeratosis, acanthosis, lacunas and spaces in the epidermis and a pronounced basal cell hyperplasia. The surface of the lesion is uneven and contains invaginations, which are filled with horny plugs. The epithelium surrounding these horny plug–filled invaginations shows the aforementioned atypical proliferation of the basal cell layer. In addition, there are pigmentary changes and minor alterations in the corium.

Most dermatologists are familiar with the hyperkeratosis and parakeratosis found in Darier's disease. These occur at both follicular and nonfollicular sites. In places, there may actually be horny plugs, which contain the so-called grains and corps ronds. In other sites the horny plugs may be in close proximity to lacunas, and there may be cystlike spaces containing corps ronds and grains. The epithelium itself (stratum granulosum and stratum spinosum) is generally thickened. The usual relation of an increased stratum granulosum or its absence at sites of hyperkeratosis or parakeratosis, respectively, is found in this disease. In the prickle cell layer one can see the widely publicized corps ronds and grains. Above the epithelial projection, there are the spaces, or lacunas, originally described by Buzzi and Miethke,[6] which Boeck[7] stated were due to a loss of cohesion of the prickle cells, permitting the formation of spaces into which fluid may enter. These spaces are of recent interest because of the discussion of Hailey and Hailey's disease (familial benign chronic pemphigus[8]). The histologic features of this disease superficially resemble those of Darier's disease, but critical examination reveals that both processes have basal cell proliferation (slight in chronic benign familial pemphigus; slight to excessive in Darier's disease) and acantholysis (extreme in the first-named disease; slight to moderate in Darier's disease). Hyperkeratosis and dyskeratosis, regularly present in Darier's disease, are absent in chronic benign familial pemphigus. There is a notable disturbance in the pigmentary function of the epidermis in Darier's disease. Some observers have noted an excess of pigment in the basal layer, while

6. Buzzi, F., and Miethke, F.: Ueber die Dariersche Dermatose, an der Hand eines selbst beobachteten Falles, Monatsh. f. prakt. Dermat. **12**:9-24; 59-71, 1891.

7. Boeck, C.: Vier Fälle von Darierscher Krankheit, Arch. f. Dermat. u. Syph. **23**:857-886, 1891.

8. Hailey, H., and Hailey, H.: Familial Benign Chronic Pemphigus, Arch. Dermat. & Syph. **39**:679-685 (April) 1939; South. M. J. **33**:477-481, 1940. Sachs, W.; Hyman, A. B., and Gray, M. B.: Epidermolysis Bullosa: A Recently Described Variant, Arch. Dermat. & Syph. **55**:91-100 (Jan.) 1947.

others (Hidaka) have observed a diminution or absence of pigment (Mu [9]). In one of the sections (1988) from the second patient with Darier's disease mentioned in this paper, there was evidence of metaplasia of the basal cells into prickle cells, the latter cells occurring at a site where basal cells should have occurred. The significance of this observation is uncertain, but the change has not been previously noted. As a rule metaplasia is infrequently recorded in dermatopathology, but Weidman [10] mentioned it in connection with the epithelial cells lining the sweat ducts in the presence of surrounding acute inflammatory processes attended by, or near, suppuration. Walther and Montgomery [11] found metaplasia in the direction of mucinous glands in the cells of the epidermis that had begun to differentiate toward sweat ducts. Stokes [12] also noted metaplasia of epithelium lining the ducts of the sweat apparatus near the cutaneous surface in his case of nevus syringocystadenomatosus papilliferus. The papillae are lengthened, shortened, hardened and flattened. In case of widespread lesions the papillae may be atrophic in the centers of the lesions and elongated at the periphery, this distribution yielding a microscopic picture of a central dell. In the corium one finds perivascular infiltration, chiefly with lymphocytes, and a scattering of plasma, mast cells and leukocytes, including eosinophils. Melczer [13] was able to demonstrate, in a case of vegetative Darier's disease, masses of plasma cells, as well as intracellular fuchsinophilic bodies, around the epithelioma-like epithelial proliferation. Changes similar to those on the cutaneous surfaces have been noted in the lesions of the mucous membrane. The details of the various changes have been thoroughly collated by Brünauer and by Miani.[14]

Of particular interest to me and to my associates, because of the papillomatous cases here presented, are the relations of the basal cell

9. Mu, J. W.: Beitrag zur Untersuchung der Pigmentverhältnisse beim Morbus Darier, Acta dermat.-venereol. **11**:365-372, 1930.

10. Weidman, F. D.: The Border Zone Between the Hyperplastic and Neoplastic Processes of Cutaneous Epithelium, Am. J. M. Sc. **165**:479-485, 1928; Metaplasia (Acute) of Sweat Duct Epithelium in Acute Suppurations, Arch. Dermat. & Syph. **10**:275-278 (Sept.) 1924.

11. Walther, M., and Montgomery, H.: Schweissdrüsentumor mit Epithelmetaplasie, Arch. f. Dermat. u. Syph. **163**:420-426, 1931.

12. Stokes, J. H.: A Clinico-Pathologic Study of an Unusual Cutaneous Neoplasm Combining Naevus Syringadenomatosus Papilliferus and a Granuloma, J. Cutan. Dis. **35**:411-425, 1917.

13. Melczer, N.: Zur Histologie der sogenannten. Darierschen Dyskeratose (Epitheliomatosis miliaris Nékám), Dermat. Wchnschr. **83**:1127-1136, 1926.

14. Miani, G.: La malattia di Darier allo stato attuale delle nostre conoscenze, Arch. ital. di dermat., sif. **15**:433-510, 1939.

layer which have long been recognized in this disease and which we wish again to emphasize to American dermatologists. It must be stressed at the onset that this basal cell proliferation is a feature of all cases of Darier's disease but becomes a highly distinctive and prominent characteristic of the vegetative cases. The basal cell layer forming the base of the lacunas no longer presents its usually orderly arrangement but shows evidence of a change superficially resembling epithelioma. There are long, small, tubelike or finger-like proliferating processes, composed of basal cells, which penetrate deep into the corium. These projections send out side branches. Lacunas are present among the proliferating interpapillary pegs. Here and there corps ronds are discernible. There may, in addition, be cells with hyalin bodies, as well as grains. Frequently the thickened basal cell layer shows numerous mitotic figures. Darier [15] had already called attention to this phenomenon of basal cell hyperplasia in his earliest publications. He made the following statement:

> I should like to add a few words concerning the exuberant lesion of the inguinal region in case 2.
>
> Section of these tubercles shows, around a dilated pilosebaceous follicle, ramifying epithelial processes separated by strands of connective tissue, the whole contituting a structure like that of a papilloma or epithelioma. The condition is evidently due to an exaggeration of the proliferation of the interpapillary epithelial processes, already referred to in connection with the smaller lesions. The excessive proliferation explains the hypertrophic character of the lesions about the pubes and the groins of man. The dilated pilosebaceous orifice is filled with sebaceous matter which contains numerous "grains" and some bacteria. The epithelial vegetations contain "round bodies."

Boeck also had demonstrated the proliferation of the interpapillary pegs which split and spread below, and Jarisch and Matzenauer,[16] in 1908, mentioned proliferations of the rete malpighii, whose projections were partly in the form of a broad club or partly drawn to a fine point and pushed on deep into the corium. Brünauer stated that gradually, however, in the presentations of various authors, the discussions of the pathogenesis of the corps ronds, grains, lacunas and fissures claimed more and more attention, and the phenomenal changes in the basal cell layers were forgotten or were considered of little significance. A revival of interest in these observations occurred in the German and Italian

15. Darier, J., in Unna, P. G.; Morris, M.; Duhring, L. A., and Leloir, H.: Internationaler Atlas von seltener Hautkrankheiten, Hamburg, L. Voss, 1893, pts. 8 and 9.

16. Jarisch, A.: Die Hautkrankheiten, revised by R. Matzenauer, ed. 2, Vienna, A. Hölder, 1908, p. 690.

literature (Fasal,[17] Kreibich,[18] Ravogli,[19] Sachs[20] and Nékám[21]). Bellini,[22] for example, spoke of new formations of tubules and cords of epithelial formation derived from the basal cell layer. Bizzozero[23] mentioned the numerous mitotic figures in the basal cell layer below the lacunas, as well as epithelial proliferation into the connective tissue at these sites. Martinotti[24] also referred to the basal cell hyperplasia, which approached a neoplasm of basal cells, and the transformation of keratinization. The whole subject was thoroughly reviewed by Pinkus and Ledermann in 1921[25] on the basis of a case, presumably the most extreme to that time, but apparently from their data much milder than either of our cases. In addition to hyperkeratosis, dyskeratosis, broadening of the papillae and changes in the cutis, these authors noted the change in the epithelium surrounding the hair follicle. The epithelium sends out processes resembling epithelioma, with lumens in their depths. The cells of these tubelike projections are cuboidal epithelial cells. These processes are at the bottom of the grotesque, luxuriant, papillary growth. Zieler and Jacobi,[26] as well as Frieboes,[27] Hamdi,[28] Kyrle[29] and Gans,[30] described similar changes in the descriptions of Darier's disease in their texts. Parallel with the changes in the skin, a similar phenomenon occurs in the mucous membranes in Darier's disease. Brünauer, in his monograph, reviewed his

17. Fasal, H.: Ein Fall von Darierscher Krankheit, Arch. f. Dermat. u. Syph. **74**:13-22, 1905.

18. Kreibich, K.: Zum Wesen der Psorospermosis Darier, Arch. f. Dermat. u. Syph. **80**:367-378, 1906.

19. Ravogli, A.: Psorospermosis cutis, Monatsh. f. prakt. Dermat. **18**:165-177, 1894; **19**:81, 1894.

20. Sachs, O.: Psorospermosis follicularis Darier, Wien. med. Wchnschr. **56**:457-462 and 570-575, 1906.

21. Nékám, cited by Melczer.[10]

22. Bellini, A.: Discheratoma nevico (psorospermosi follicolare vegetante di Darier), Gior. ital. d. mal. ven. **55**:776-823, 1914.

23. Bizzozero, E.: Ueber die Dariersche Dermatose, Arch. f. Dermat. u. Syph. **93**:73-84, 1908.

24. Martinotti, cited by Brünauer.[3]

25. Pinkus, F., and Ledermann, R.: Beitrag zur Histologie und Pathogenese der Darierschen Krankheit, Arch. f. Dermat. u. Syph. **131**:360-377, 1921.

26. Zieler, K. W. F., and Jacobi, E.: Lehrbuch und Atlas der Haut- und Geschlechtskrankheiten für praktische Aerzte und Studierende, Vienna, Urban & Schwarzenberg, 1924.

27. Frieboes, W.: Grundriss der Histopathologie der Hautkrankheiten, Leipzig, F. C. W. Vogel, 1921.

28. Hamdi, H.: Morbus Darier, Virchows Arch. f. path. Anat. **279**:237-243, 1930.

29. Kyrle, J.: Vorlesungen über Histobiologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1925.

30. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925.

own and others' experience in dealing with this characteristic proliferation of the basal cell layer of the skin and mucous membranes.

It is somewhat surprising that the proliferation of basal cells in Darier's disease is given so little notice by American dermatologists.

Since Morrow [31] in 1894 called attention to Darier's findings with regard to the vegetations in the inguinal region, which histologically resembled "an epithelioma having its origin in the follicle," few later American texts have stressed this feature of the histology of this disease. Mention of it is, for example, entirely lacking in the works of Andrews,[32] Sutton and Sutton,[33] Ormsby and Montgomery [34] and Knowles, Corson and Decker.[35] McCarthy,[36] on the other hand, in his volume on histopathology, made the following statement:

> The epithelium as a whole appears somewhat thickened. That portion of the epithelium which surrounds the horn-filled invaginations has a tendency to atypical proliferation in the form of rete cones either rounded on their ends or drawn out to a point. These cones often penetrate fairly deeply into the corium and although they produce a picture very suggestive of epitheliomatous growths, no cases resulting in malignancy have been reported. This finger-like proliferation of the rete cones is considered very typical of Darier's disease.

Frost,[37] as well as Pinkus and Epstein,[38] also recently noted, in passing, the basal cell proliferation in Darier's disease. Goodman,[38a] on the basis of his experience, stated the belief that hyperplasia of basal cells is the most prominent feature of Darier's disease.

Part of the reason for this general lack of emphasis on the basal cell proliferation in American literature is probably, as Wile [39] indicated, the result of the fact that in most of the cases observed and described in this country the disease is much milder than it is in ones

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31. Morrow, P. A.: A System of Genito-Urinary Diseases, Syphilology and Dermatology, New York, D. Appleton & Company, 1894, vol. 3, pps. 628-633.

32. Andrews, G. C.: Diseases of the Skin, ed. 3, Philadelphia, W. B. Saunders Company, 1946.

33. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939.

34. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943.

35. Knowles, F. C.; Corson, E. F., and Decker, H. B.: Diseases of the Skin, ed. 4, Philadelphia, Lea & Febiger, 1942.

36. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931.

37. Frost, K.: Dyskeratosis Follicularis (Darier's Disease), Arch. Dermat. & Syph. **31**:508-511 (April) 1935.

38. Pinkus, H., and Epstein, S.: Familial Benign Chronic Pemphigus: Report of Case, Arch. Dermat. & Syph. **53**:119-124 (Feb.) 1946.

38a. Goodman, M. H., in discussion on Frank and Rein.[54]

39. Wile, U. J., in discussion on Chambers, S., and Anderson, S.: Keratosis Follicularis (Darier), Arch. Dermat. & Syph. **39**:358 (Feb.) 1939.

seen abroad. A survey of the cases of Darier's disease presented in the various local and national dermatologic societies in America, as reported in the ARCHIVES (1920-1946), reveals that about 10 of 120 cases reported showed papillomatous lesions. There was no mention of the pseudoepitheliomatous change in the histologic reports of any of these cases. On the other hand, although 2 of 9 cases of Darier's disease reported at the Copenhagen Congress of Dermatology and Syphilology in 1930 were of the vegetative type, this form is now rated as being of rare occurrence even in France (Perin [40]).

Although dysplasia of basal cells and proliferation of epithelioma-like proportions histologically occur in Darier's disease, no really authentic case of secondary development of carcinoma has been reported. Wende's [41] patient obviously had multiple epitheliomatosis, probably of arsenical origin (Montgomery [42]). Charache's [43] case likewise, although studied by a competent general pathologist, was not documented by histologic illustrations. A small lymph node was excised from the inguinal region, and concerning the specimen it was simply stated that a diagnosis was made of Darier's disease with malignant transformation. Occurrence of Darier's disease associated with epithelioma of the nose, reported by Wise and Parkhurst [44] and by Streitmann,[45] represents coincidental, and not related, processes.

We believe that the basal cell changes in Darier's disease do not differ essentially from the now widely recognized epithelial response to a stimulus, which response is variously known as benign penetrating epithelium (Broders [46]) or pseudoepitheliomatous hyperplasia (White and Weidman [47]). The epithelial cells in this state, although they may penetrate far beyond the normal level of the dermoepidermal junction

40. Perin, L.: Maladie de Darier, in Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson et Cie, 1936, p. 392.

41. Wende, G. W.: Keratosis Follicularis Resulting in Multiple Epithelioma: Report of a Case, J. Cutan. Dis. **26**:531-551, 1908.

42. Montgomery, H.: Arsenic as an Etiologic Agent in Certain Types of Epithelioma: Differential Diagnosis from, and Further Studies Regarding, Superficial Epitheliomatosis and Bowen's Disease, Arch. Dermat. & Syph. **32**:218-236 (Aug.) 1935.

43. Charache, H.: Darier's Disease with Malignant Transformation, Arch. Dermat. & Syph. **35**:480-484 (March) 1937.

44. Wise, F., and Parkhurst, H. J.: Notes on Two Unusual Cases of Darier's Disease, Arch. Dermat. & Syph. **2**:430 (Oct.) 1920.

45. Streitmann, Morbus Darier, Zentralbl. f. Haut- u. Geschlechtskr. **55**:616, 1937.

46. Broders, A. C.: Carcinoma in Situ Contrasted with Benign Penetrating Epithelium, J. A. M. A. **99**:1670-1674 (Nov. 12) 1932.

47. White, C., and Weidman, F. D.: Pseudo-Epitheliomatous Hyperplasia at the Margins of Cutaneous Ulcers, with Especial Reference to Histologic Diagnosis, J. A. M. A. **88**:1959-1963 (June 18) 1927.

and may be greatly increased in number, have retained for the most part the characteristics of normal epithelial cells.

Pseudoepitheliomatous hyperplasia in chronic inflammation has long been difficult to differentiate from cancer of the skin. More difficult of distinction is the grade 2 or 3 hyperplasia seen occasionally at the edge of chronic ulcers, but especially in verrucous lesions, as typified by bromoderma. Narrow strands of epithelial cells, containing numerous mitotic figures, are seen penetrating deeply into the cutis. Except for the mitosis, however, the epidermal cells contained in these strands present none of the features of malignant cells, such as changes in nucleoli and an increase in the size of the nucleus in relation to the amount of cytoplasm (MacCarty [48]). Furthermore, these narrow epithelial strands are invaded by leukocytes with apparent disintegration of some of the epidermal cells, a phenomenon which usually is not seen in the narrow strands of squamous cell epithelioma, grade three or four, though in the latter the strands may be surrounded by a dense infiltrate. White and Weidman emphasized that every gradation up to perfect imitation of epithelioma may occur, so that it becomes impossible to distinguish histologically between squamous cell epithelioma and nonmalignant hyperplasia. These authors stated the belief that a diagnosis of carcinoma is not justified unless the infiltration extends to the level of the sweat glands or farther or unless the pathologist has had wide acquaintance with the behavior of hyperplastic epidermis in general. Winer,[49] in his review on this subject, summarized the diagnostic characters which have been reported to differentiate hyperplasia from true cutaneous carcinoma. He expressed the conclusion that the most frequently noticed histologic change was edema of the upper part of the cutis and in the epidermis of all the sections which showed pseudoepitheliomatous hyperplasia. The edema caused vacuolation of the intercellular spaces in the lower portion of the epidermis and disintegration and vacuolation of the epidermal cells in the upper part of the epidermis. Although the edema was diffuse, the pseudoepitheliomatous proliferation was, as a rule, localized to a single area. Therefore, the factor of nutrition must be considered in the search for a possible cause of the hyperplasia. This epithelial change has been noted in a number of cutaneous diseases, to which Darier's disease must be added.

When one makes a histologic comparison between the pseudoepitheliomatous changes in Darier's disease and those in epithelioma, one

48. MacCarty, W. C.: Identification of the Cancer Cell, J. A. M. A. **107**:844-845 (Sept. 12) 1936.

49. Winer, L. H.: Pseudoepitheliomatous Hyperplasia, Arch. Dermat. & Syph. **42**:856-867 (Nov.) 1940.

notes that there are a number of similarities. Both may contain basal cell proliferation; both, as well as other diseases (Meierowsky [50]), may contain dyskeratotic cells, and both may contain fissures and lacunas.

Although Darier's disease has been known to occur or become aggravated after acute infections and other irritative processes, such as furunculosis, croup, erysipelas, variola, vaccination, ptomaine poisoning and sunlight (Preissmann [51]), these disorders can hardly be the basis for the long-continued, intermittent course of the process. The presence of the Koebner phenomenon in Darier's disease, as demonstrated by Bettmann,[52] suggests that there may still be a fundamental relation between Hailey and Hailey's [8] disease (Pels and Goodman [53]) and Darier's disease, since Frank and Rein [54] found a definite response to trauma in the cases which they studied.

In the interpretation of the histologic features of Darier's disease, the relation of the process to the cutaneous appendages (sweat and pilosebaceous) is of importance. At times one finds lesions of this disease in the proximity of, or actually surrounding, a hair follicle. This fact undoubtedly originally led Darier,[55] as well as White,[56] to the idea that the process was follicular. Numerous others have shown the lesions to be extrafollicular (observations collected by Miani and by Brünauer). For example, Ellis,[57] in his review, expressed the opinion that Darier's disease is a benign dyskeratosis, which incidentally affects the hair follicles. Hidaka, who also found no relation of the lesions to the hair follicle in the majority of the cases, showed that 112 of 163 lesions (68.6 per cent) were nonfollicular; 50 lesions (30.7 per cent) were near follicles, and only 1 lesion was actually peri-

50. Meierowsky, E: The Paget Cell: Its Structure, Occurrence and Significance, Proc. Roy. Soc. Med. **38**:495-499, 1945.

51. Preissmann, M.: De l'action provocatrice de la lumière dans la maladie de Darier: Étude histologique des efflorescences provoquées expérimentalement en peau saine par les rayons ultra-violets, Ann. de dermat. et syph. **6**:188-203, 1946.

52. Bettmann: Ueber Umbauvorgänge als Ausdruck spezifischer Reaktionsfähigkeit bei Hautkrankheiten (Die Reizbarkeit der Haut bei der Darierschen Krankheit), Arch. f. Dermat. u. Syph. **135**:65-76, 1921.

53. Pels, I. R., and Goodman, M. H.; Criteria for the Histologic Diagnosis of Keratosis Follicularis (Darier): Report of a Case with Vesiculation, Arch. Dermat. & Syph. **39**:438-455 (March) 1939.

54. Frank, S. B., and Rein, C. R.: Dyskeratoid Dermatosis, Arch. Dermat. & Syph. **45**:129-151 (Jan.) 1942.

55. Darier, J.: De la psorospermose folliculaire végétante, Ann. de dermat. et. syph. **10**:597-612, 1889.

56. White, J. C.: A Case of Keratosis (Ichthyosis) Follicularis, J. Cutan. & Genito-Urin. Dis. **7**:201-209, 1889.

57. Ellis, F. A.: Keratosis Follicularis Is Not Primarily a Follicular Disease, Arch. Dermat. & Syph. **50**:27-30 (July) 1944.

follicular. The response or lack of response of Darier's disease to vitamin A therapy, noted by a host of recent writers (Jeghers,[58] Peck and associates,[59] Carleton and Steven [60] and Pettler [61]) does not argue for or against the follicular character of the dermatosis. The patient of the second case described herein received massive doses of vitamin A without material benefit. A strong argument against the follicular nature of Darier's disease is the occurrence of lesions on the mucous membranes, where hair follicles do not usually exist (Kren,[62] Spitzer,[63] and Brünauer). One is mindful of the ever present possibility of aberrant hair follicles, analogous to the sebaceous glands found on the mucous membrane in Fordyce's disease.

Similarly, there is practically no evidence that Darier's disease is a lesion of the sweat glands, although there have been a number of investigators who have supported this idea (Wende, Ormerod and MacLeod,[64] Jordan,[65] Bukovsky,[66] Buzzi and Miethke and C. Boeck). Hidaka showed, however, that in 121 of 163 lesions (74.2 per cent) there was no relation, in 36 lesions (23.9 per cent) there was close proximity to sweat apparatus and in 3 cases there were sweat glands opening in the center of the lesion, though there was no hyperkeratosis in these glands. In a process as extensive as those in our cases, it is hardly likely that many lesions could escape being close to sweat apparatus. This fact does not, however, indicate that the sweat apparatus was necessarily participating in the changes. My associates and my failure to demonstrate myoepithelium in the finger-like processes projecting into the lacunas is only negative evidence against origin from the sweat glands, since in undoubted lesions of the sweat glands the myoepithelium may be absent.

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58. Jeghers, H.: Skin Changes of Nutritional Origin, New England J. Med. **228**:678-686 and 714-723, 1943.

59. Peck, S. M.; Chargin, L., and Sobotka, H.: Keratosis Follicularis (Darier's Disease): A Vitamin A Deficiency Disease, Arch. Dermat. & Syph. **43**:223-229 (Feb.) 1941.

60. Carleton, A., and Steven, D. M.: Keratosis Follicularis: A Study of Four Cases, Arch. Dermat. & Syph. **48**:142-150 (Aug.) 1943.

61. Pettler, M. F.: The Effect of Vitamin A in Pityriasis Rubra Pilaris and Keratosis Follicularis, Pennsylvania M. J. **45**:604-605, 1942.

62. Kren, cited by Brünauer.[3]

63. Spitzer, R.: Zur Kenntnis der Darierschen Krankheit, Arch. f. Dermat. u. Syph. **135**:362-376, 1921.

64. Ormerod, J. A., and MacLeod, J. M. H.: On a Case of Darier's Disease, Brit. J. Dermat. **16**:321-334, 1904.

65. Jordan, A.: Fall von Darier, abstracted, Dermat. Wchnschr. **58**:150, 1914; Die Dariersche Krankheit, ibid. **73**:889-900, 1921.

66. Bukovský, J.: Psorospermosis follicularis vegetans Darier, Arch. f. Dermat. u. Syph. **75**:279-302, 1905.

It is logical to assume for Darier's disease, on the question of whether the process originates from the surface or from a sweat gland or hair follicle, the same reasoning proposed by Weidman [67] to explain the occurrence in the same person of epithelial tumors apparently arising from all three; this theory is, namely, that all are derived from the same embryonic source, which is at first neither sweat duct, epidermis nor hair follicle. If the potentialities for formation of a tumor in one of these embryonic sources which has remained undifferentiated develop into sudoriferous or pilary structure, the Krompecher tumor will appear; if the tumor occurs at a later time in the development of the source, a tumor of the sweat glands may result, or, if development occurs when the hair follicle is developing, a tumor of the hair follicle will be expected. If the lesion occurs at the time of full differentiation, all three types of involvement may be present in the same lesion (multicentric). In the application of this explanation of the various types of involvement in Darier's disease, it is assumed that one is dealing with a nevic state, as many have maintained.

DIFFERENTIATION FROM NEVUS OF SWEAT GLANDS

Only occasionally is Darier's disease mistaken clinically for a systematized verrucous nevus. In such cases histologic study should afford the means of final differentiation, but, as was previously noted, a lesion of the sweat glands (nevus syringocystadenomatosus papilliferus) was considered by some for a while to be the correct histologic interpretation of 1 of our cases. We believe this interpretation to be incorrect, on both clinical and histologic grounds.

In the general literature of tumors, the name for a papillary growth of variable structure and uncertain nosology is hidradenoma papilliferum. In dermatologic literature, however, this type of lesion is known either as nevus syringadenomatosus papilliferus (Werther [68]) or as nevus syringocystadenomatosus papilliferus, a designation for which there are no clearcut grounds (Caro [68a]). This usually solitary and slowly growing tumor occurs on the genitalia, perineum, thighs and face and scalp (sites of predilection of Darier's disease). The clinical characteristics of the process are well described by Frieboes, as cited by Sachs and Lewis [69]:

67. Weidman, F. D., in discussion on Stillians, A. W.: Nevo-Epithelioma Adenoides (Cylindroma) of the Scalp, Arch. Dermat. & Syph. **27**:481-489 (March) 1933.

68. Werther, L.: Syringadenoma papilliferum (Naevus syringadenomatosus papilliferus), Arch. Dermat. u. Syph. **116**:865-870, 1913.

68a. Caro, M. R.: Personal communication to the author.

69. Sachs, W., and Lewis, G. M.: Naevus Syringadenomatosus Papilliferus (Werther): Report of Five Cases, Arch. Dermat. & Syph. **36**:1202-1209 (Dec.) 1937.

The favorite sites are the shoulders, the axillae, the genito-inguinal and surrounding regions and the hairy portion of the scalp. The lesions are rose-red papules of firm consistency from the size of a millet seed to that of a hemp seed, usually arranged in groups. Owing to their transparent nature, one or more vesicle-like inclusions may often be distinguished; these inclusions are from the size of a pin-point to that of a pin-head and filled with clear fluid. In addition, the papules are umbilicated at their summit, being similar to lesions of molluscum contagiosum. (Because of this finding, solitary lesions of long duration clinically resembling lesions of molluscum contagiosum may prove to be nevi of the type under consideration.) The papules stand out discretely or form directly confluent plaques. In one case (Kreibich [70]) papillary growths were observed on the surface of such a plaque.

Elliot [71] in 1893 described a linear (systematized) lesion. Occasionally the lesion may become malignant (Horn [72]).

Not infrequently the tumor extends through the whole thickness of the corium; rarely it arises near the epidermis. The sweat glands are somewhat dilated and the sweat ducts cystic in places. The inner surface of the cavity of the duct contains small, villus-like projections. The lining is composed of two or more layers of cells, including an outer columnar and inner cuboidal layer. The epidermis is acanthotic; there may or may not be an associated inflammatory reaction. Stokes reported a reaction suggestive of granuloma pyogenicum or vegetative dermatitis with plasma cells. The nature of the lesion is not definitely known, and it has been considered congenital by some. Other associated cutaneous lesions of an inflammatory nature have suggested a reactive process.

Stokes reported the first American case under the title of nevus syringadenomatosus papilliferus. Comprehensive reviews (Nödl,[73] Sachs and Lewis, Mayer,[74] Reuterwall,[75] Plantevin [76] and Biberstein [77]) of this subject are based on relatively few cases. My associates and I

70. Kreibich, cited by Frieboes,[27] p. 186.

71. Elliot, G. T.: Adeno-Cystoma Intracanaliculare Occurring in a Naevus Unius Lateris, J. Cutan. Dis. **11**:168-173, 1893.

72. Horn, R. C., Jr.: Malignant Papillary Cystadenoma of Sweat Glands with Metastases to the Regional Lymph Nodes, Surgery **16**:348-355, 1944.

73. Nödl, F.: Beitrag zum Naevus syringo-cystadenomatosus papilliferus, Arch. f. Dermat. u. Syph. **178**:697-713, 1939.

74. Mayer, I.: Zur Histologie der Hidroadenome, Frankfurt. Ztschr. f. Path. **55**:548-590, 1941.

75. Reuterwall, O.: Naevus Syringo-Cystadenomatosus Papilliferus and Its Relation to Malignancy, Acta. path. et. microbiol. Scandinav., 1933, supp. 16, pp. 376-387.

76. Plantevin, P.: L'hidradénome verruqueux fistulo-végétant: Etude des malformations et états précancéreux de la peau, Thesis, Paris, Amédée Le Grand, 1927.

77. Biberstein, H.: Ueber papilliforme Syringocystadenome, Arch. f. Dermat. u. Syph. **152**:602-610, 1926.

Fig. 11 (case 3).—Nevus syringocystadenomatosus papilliferus. Note relation to sweat apparatus and intraductal epithelial proliferation in addition to the large cyst opening to the surface; compare with fig. 8 (slide 63; × 16).

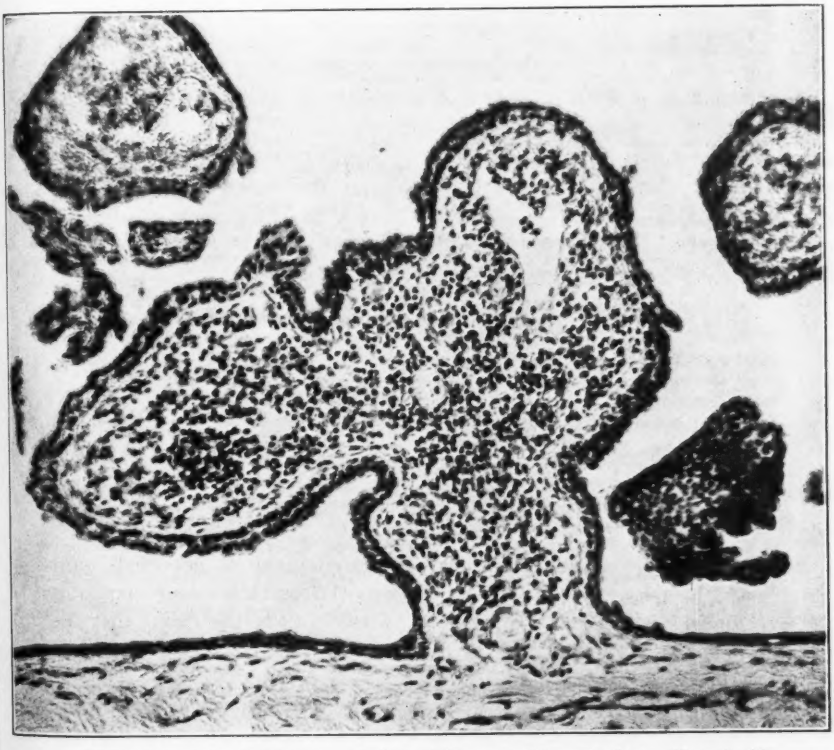

Fig. 12 (case 3).—Higher power view of "intracystic" projections. Note double layer of epithelial cells: inner, cuboidal, and outer, columnar (slide 63; × 235).

have encountered but 1 example among 3,000 specimens for biopsy taken from cutaneous lesions and submitted to our laboratory.

CASE 3.—L. N., a white deaf-mute aged 20, on Nov. 2, 1931, presented above his right ear a sharply localized granulomatous lesion with eroded top, irregular in outline and associated with several flat-topped satellite lesions. This process had begun when the patient was 1 year old, and it had not grown much in size. The clinical diagnosis was granuloma, but histologically the lesion showed typical

Histologic Comparison of Darier's Disease and Nevus Syringocystadenomatosus Papilliferus

	Darier's Disease	Nevus Syringocystadenomatosus Papilliferus
Hyperkeratosis	Massive	Usually absent
Parakeratosis	May be extreme in places	Usually absent
Dyskeratosis Corps ronds Grains	Present	Absent
Lacunas	Characteristic	Absent
Basal cell proliferation	Constant, round lacunas; in papillomatous cases, extreme pseudoepitheliomatous change involving prickle cell metaplasia	Rare indeed; when present suggests epithelioma of basal cells
Papillary excrescences	Short, compact, and involved; project into lacunas; covered with one or more cell layers	Variously long and dendritic; may project on surface or into cysts; may be on remnants of walls of confluent cysts; covered with only two layers of cells
Relation to appendages and sweat apparatus	Questionable	Essential part; may be intracanalicular proliferations of epithelium of cystic duct (not apocrine glands)
Relation to pilosebaceous apparatus	Present in some cases	None
Pigmentation	Disturbance in epidermal pigmentary function; early, stimulation and proliferation; later, feeble; more pronounced near edges of epidermal overgrowths	May be present in chromatophores near the edge of the lesion
Location	Superficial in the usual case; deep in papillomatous cases	Both superficial and deep in cutis
Cyst contents	No cysts	Cellular detritus
Cyst opening	.....	Bottle-like; narrow neck
Myoepithelium	None	Sometimes present
Malignant change	Rare, if ever	Occasional
Plasma cells	May be present	May be present

features of nevus syringocystadenomatosus papilliferus (see figs. 11 and 12). Recurrence after removal occurred within fourteen years (December 1945).

While the nature of this usually benign tumor is not clear, most authorities have agreed that it is derived from the sweat apparatus (Dörffel [78]). Gates, Warren and Warvi [79] made the claim that the

78. Dörffel, J.: Naevus syringo-cystadenomatosus papilliferus, Dermat. Wchnschr. **99**:1318-1324, 1934; Zur Histogenese des Naevus syringo-cystadenomatosus papilliferus, ibid. **100**:229-231, 1935.

79. Gates, O.; Warren, S., and Warvi, W. N.: Tumors of Sweat Glands, Am. J. Path. **19**:591-631, 1943.

epithelium is not characteristic of either the gland or the duct. A reason may be that the lesion is composed of embryonal sweat apparatus (Plantevin). Biberstein could not find the iron that would be expected in the tissue if the lesion were composed of apocrine glands. Because a number of reports have stressed the presence of myoepithelium in sweat gland tumors (Mayer, Sheldon [80] and Way and Memmesheimer [81]), I have hoped that demonstration of these characteristic cells might be a definitive means of differentiation between hypertrophic Darier's disease and tumors of the sweat gland. Efforts in this direction have failed, a fact which Gates and her colleagues stated was probably not significant. A comparison of the histologic changes occurring in this process and in Darier's disease is given in the accompanying table.

SUMMARY

1. Because of the need for histologic differentiation of hypertrophic Darier's disease from nevus syringocystadenomatosus papilliferus, a review is made of the basic histologic features of Darier's disease, especially of the papillomatous form, and criteria are suggested for the histologic separation of the two processes.

2. From the clinical standpoint there is little difficulty in distinguishing hypertrophic Darier's disease from nevus syringocystadenomatosus papilliferus, since the former is a disease of wide distribution and is composed of characteristic lesions. The latter has usually a single lesion or a single group of lesions, likewise of fairly characteristic type.

3. Histologically, Darier's disease is essentially an epithelial process and shows peculiar cell degenerations (dyskeratoses), corps ronds and grains, hyperkeratosis and parakeratosis, acanthosis, lacunas and spaces in the epidermis and, especially in the hypertrophic form, a pronounced basal cell hyperplasia. It is this last feature which has led to the histologic diagnosis of carcinoma in a specimen from a patient with a disease which rarely, if ever, becomes malignant.

4. Nevus syringocystadenomatosus papilliferus shows little, if any, hyperkeratosis and parakeratosis, dyskeratosis, lacunas and basal cell proliferation. On the other hand, it is a lesion of the sweat apparatus and shows regularly intracystic papilliferous projections, which are covered with two layers of cells; the outer, columnar, and the inner, cuboidal.

University of Pennsylvania School of Medicine.

80. Sheldon, W. H.: The Myoepithelium in Sweat Gland Tumors: Distribution, Histology, Embryology and Function, Arch. Path. **31**:326-337 (March) 1941.

81. Way, S. C., and Memmesheimer, A.: The Sudoriparous Glands: I. The Eccrine Glands, Arch. Dermat. & Syph. **34**:797-808 (Nov.) 1936.

ABSTRACT OF DISCUSSION

DR. FRANCIS A. ELLIS, Baltimore: Since I was one of the dissenters from the diagnosis of hypertrophic Darier's disease in case 1 when it was presented in 1940, Dr. Weidman permitted me to have a section for study.

The slide was shown several times to the Baltimore group of dermatologists and sent to five nationally known dermatohistopathologists. Dr. Hermann Pinkus was the only one who made the diagnosis without the aid of the clinical history. His father, Dr. Felix Pinkus, had previously reported a similar case.

Dr. Beerman also sent us sections from his second case. It was the extreme pseudoepitheliomatus hyperplasia and the proliferation of the basal layer, forming acini and villi, which suggested the diagnosis of nevus syringocystadenomatosus papilliferus, but finally, after more careful studies had been made, it was these same features which confirmed the diagnosis of hypertrophic Darier's disease.

It should be emphasized that the cells lining the acini in hypertrophic Darier's disease are usually composed of a single layer of cells resembling basal cells, but, in the nevus of the sweat glands, there are two rows of cells, such as are seen in an apocrine sweat gland.

In studies of the so-called bullous Darier's disease, emphasized by Pels and Goodman and Hailey and Hailey, this feature of the formation of acini covered by one layer of cells resembling basal cells was also found. The acini or villi will be present in the dry or vesicular form if the three following features are present: proliferation of the basal layer, formation of lacunas and the more extreme stages of acanthosis (hypertrophy).

The presence of these features in the vesicular type has not been stressed previously, but they were observed in about half of the biopsies made by my associates and me and were especially prominent in a specimen taken from a patient who had hypertrophic lesions in the groin.

Again it should be emphasized that in the vesicular type the pathologic changes are usually not follicular but tend to miss the follicles; that is, they approach the neck of the adnexa and then stop. The moist type is therefore similar in these two respects to the dry form but differs histologically in the lack of dyskeratosis and the associated alterations.

We have never observed histologically in epidermolysis bullosa the typical lacunas which are found in the bullous form of Darier's disease.

I wish that Dr. Beerman would discuss in more detail why lacunas occur. Can the rete cells rejoin so that one at times can see a fairly normal epidermis above the lacunas? The degree of unalteration in the rete layer above the lacunas is one of the striking differential features between the two types; the bullous form tends to have a more normal intact prickle cell layer.

DR. C. GUY LANE, Boston: Just a short time ago I saw at one of the state hospitals in Massachusetts a patient whose case fits into the picture of hypertrophic Darier's disease. This woman, who was 74 years old, was the oldest patient with Darier's disease that I have seen. She had had Darier's disease all her life, and her father also had had the same diagnosis. Earlier, she had been sent into another state hospital—a hospital for patients with cancer—because of growths in various places on her skin. The principal lesion was an oval, moist, papillary lesion, 5.0 by 2.5 cm. in area, in her right groin. She had several other hyperkeratotic lesions on the lower part of her back and on the pubic region, as well as many follicular hyperkeratotic lesions of the face, ears and upper portion of the trunk. There was some enlargement of the ears, and there was also a pronounced cutis verticis gyrata of her forehead.

DR. FRED D. WEIDMAN, Philadelphia: Dr. Beerman has brought us a number of messages. One is that the disease may be mistaken for epithelioma, and there has been sufficient elaboration of that. A second difficulty in histologic diagnosis arises only when the papillomatous cases of Darier's disease reach an extremely exaggerated form. It is not until the papillae become most bizarre that the cells which cover them will approach the character of those that are seen in nevus syringocystadenomatosus.

While I was sitting here I was wondering what was going through Dr. McKenna's mind—whether, in his opinion, we Americans have been making a mountain out of a molehill, because Europeans know these conditions so well. Dr. Beerman indicated that this exaggerated form is known in Europe as well as over here, but that, as has been the case in America, not very much has been published. I should like to hear from Dr. McKenna on that point.

It might occur to probably almost anybody that deficiencies in the diet are responsible. At least, that theory would be the easiest way out, namely, that vitamin A deficiency would account for the difference in the incidence in Europe and in America. We must remember, though, that concerning deficiency or other factors, even though attributing a condition to a certain thing would be easy or even logical, it need not necessarily be the true solution. It must be remembered that when considering the role of geography one also has to consider the part played by the differences in race and racial characteristics. For example, all of us present know the controversy as to whether yaws is an entity or whether it is syphilis modified by race. Again, in pinta there is a disease of different appearance in Cuba and in Mexico. The question is left open as to whether or not the factor of race is responsible for the clinical differences. In hypertrophic Darier's disease, similarly, it need not necessarily be a vitamin deficiency, but the factor of race, that determines the clinical differences.

DR. ROBERT M. B. MCKENNA, London, England: I should say that Darier's disease is not common in England, at the present time, at any rate. The incidence does not seem to be increasing in any way.

As for making comments on Dr. Beerman's paper, I should like very much to discuss it, but I am afraid I am not prepared.

DR. HOWARD HAILEY, Atlanta, Ga.: I just want to make a correction. The names of Hailey and Hailey have never been connected with Darier's disease but are associated with familial benign chronic pemphigus. In the report on the condition under that title, as the senior author I stated and tried to emphasize that this condition is familial, benign and chronic. The disease disappears, leaving no clinical evidence other than temporary pigmentation. Recurrences follow at widely varying intervals, and, as the years go by, subsequent attacks become milder and are separated by longer intervals.

DR. HERMAN BEERMAN, Philadelphia: I want to express my appreciation to the various discussers, especially Dr. Weidman and Dr. Ellis.

With regard to the formation of lacunas, I am sorry, but I do not know how they form.

There are variations of opinion as to the influence of vitamin A on Darier's disease. Some people think that patients having Darier's disease are helped by the use of vitamin A. The second patient mentioned herein received 250,000 units of vitamin A a day for a long time. I put the statement that way because I do not know exactly how long, since he was in the medical service, records of which were not available, for part of the time.

I want to apologize to the men from Boston for not having called Darier's disease White's disease; since the former is the more commonly used term, I have employed it.

ESSENTIAL HIRSUTISM

Dermatologic and Endocrinologic Considerations

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HIRSUTISM in women is common. Most hirsute patients come to the physician because of vanity, complaining of the cosmetic inelegance of excessive hair. The psychic trauma of hirsutism, particularly when the condition involves the face, is striking. Even the bearded lady of the sideshow is often miserable, despite her superficial attitude of amusement.

It is because of this psychic trauma, the cosmetic appearance and the many misconceptions of the role of the endocrine glands in the development of hirsutism that we have evaluated our material. It is hoped that these data may somewhat clarify the problem.

To understand better abnormal hair growth, one should know normal hair growth. Bissell and Williams [1] discussed hirsutism in women, and Danforth [2] recently reviewed the physiology of human hair.

Before discussing normal and abnormal hair growth of the human being, we shall review the results of some animal experiments. Undernourished normal rats had delayed growth of hair, although skeletal growth continued.[3] On the other hand, well fed adrenalectomized rats [4]

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Read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 25, 1948.

1. Bissell, G. W., and Williams, R. H.: Hirsutism in Females: A Clinical Study of Its Etiology, Course and Treatment, Ann. Int. Med. **22**:773 (June) 1945.

2. Danforth, C. H.: Physiology of Human Hair, Physiol. Rev. **19**:94 (Jan.) 1939.

3. Butcher, E. O.: Hair-Growth in Young Albino Rats in Relation to Body Size and Quantity of Food, J. Nutrition **17**:151 (Feb.) 1939.

4. Butcher, E. O.: Hair Growth in Adrenalectomized and Adrenalectomized Thycrin Treated Rats, Am. J. Physiol. **120**:427 (Nov.) 1937.

demonstrated precocious hair growth. In poorly fed, undernourished rats with adrenal hypertrophy, adrenalectomy resulted in increased growth of hair, which began within forty hours after the operation.[5] Administration of estrogens retarded hair growth in rats, dogs and guinea pigs.[6] This retardation of hair growth in rats could be prevented by the concomitant administration of androgens.[6b] Plumage of birds, which is analogous to hair, was affected by gonadectomy.[7] Removal of the thyroid and pituitary glands also influenced the growth of hair in various animals.

One of the most obvious differences between hair growth in the animal and that in the human being is its development on contiguous body areas of man. Danforth [2] stated that, although humoral control of human hair growth probably exists, the end product of each hair follicle is determined chiefly by constitutional factors within the hair cells. It appears that some hair follicles are unaffected by the humoral differences of the male and the female, whereas others may be profoundly affected. There apparently is a constitutional gradient which causes individual hair follicles to respond to hormonal influence. Bissell and Williams [1] suggested that this constitutional characteristic may explain why two morphologically identical follicles may both give a fine body hair growth until puberty, when the product of one follicle may change to long terminal hair, although the product of the other follicle may not change throughout life.

Danforth [2] offered the following classification of hair: (1) general body hair (lanugo), which is uninfluenced by endocrine factors; (2) ambosexual hair of males and females, which is dependent on hormone stimulation and is apparently equivalent in the two sexes, pubic hair and axillary hair being examples of this type, and (3) truly sexual hair, which is represented by the beard of the male and, less clearly, by the terminal hair of the shoulders, of the anterior portion of the chest and of the abdomen. The pattern of the hair of the head is probably a secondary sexual characteristic, as Bernstein and Robertson [8] showed that the weight per unit of hair length is greater in the male.

5. Butcher, E. O., and Richards, R. A.: Relation of Adrenals to Retarded Hair Growth in Underfed Albino Rats, Endocrinology **25**:787 (Nov.) 1939.

6. (*a*) Gardner, W. U., and Devita, J.: Inhibition of Hair Growth in Dogs Receiving Estrogens, Yale J. Biol. & Med. **13**:213 (Dec.) 1940. (*b*) Hooker, C. W., and Pfeiffer, C. A.: Effects of Sex Hormones upon Body Growth, Skin, Hair and Sebaceous Glands in Rat, Endocrinology **32**:69 (Jan.) 1943.

7. Allen, E.; Danforth, C. H., and Doisy, E. A.: Sex and Internal Secretions, ed. 2, Baltimore, Williams & Wilkins Company, 1939.

8. Bernstein, M., and Robertson, S.: Racial and Sexual Differences in Hair Weight, Am. J. Phys. Anthropol. **10**:379 (July-Sept.) 1927.

Hamilton [9] described a masculine trait which distinguishes absolutely between normal men and women. This character is the growth of terminal (coarse) hairs on the external ear. Three factors control development of this trait: aging, endocrine stimulation (apparently androgenic) and gonadal predisposition. Large auricular hairs grow in Caucasian men after the twenty-fourth year and increase in frequency and coarsen until about the fifty-fifth year; 75 per cent of the men studied exhibited this character. Terminal hairs were not observed in a series of 105 women and 50 eunuchs. Auricular hair appeared in 3 of 5 eunuchs receiving androgenic treatment and in 3 of 5 women with pronounced virilism. Pronounced hairiness depends on age and inheritance more than on any degree of androgenic stimulation. Titers of urinary steroids in 57 normal Caucasian men bore no quantitative relation to the amount of auricular hair.

The endocrine glands which are chiefly concerned with hair production are the adrenal glands (cortex), the gonads, the thyroid and the anterior lobe of the pituitary.[10] Prepuberal castration does not affect the appearance of ambosexual hair. Since androgen therapy increases the size and number of pubic sebaceous glands of prepuberal boys, there apparently exists a synergism between the gonads and the adrenals in ambosexual hair growth in males.[11] Means [12] stated that ambosexual hair of both sexes and the beard of males are diminished or absent in myxedema. This may be due to the lowered metabolism, which may affect not only growth of individual hair follicles but also the functions of related endocrine glands. The persistence of axillary and pubic hair after the menopause indicates the absence of any correlated ovarian influences. Prepuberal ovariectomy results in the nonappearance of axillary and gynecoid pubic hair. An ultimate hyperfunction of the pituitary and sequential adrenal hyperactivity, however, may be followed by growth of axillary and android pubic hair. Prepubescent females with Addison's disease who have adequate function of the ovaries and of the anterior lobe of the pituitary function or females with panhypopituitarism do not have pubic or axillary hair.

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9. Hamilton, J. B.: A Secondary Sexual Character That Develops in an Organ Common to Both Sexes, but Normally Only in Men, with a Discussion of the Relation of this Character to Endocrine Stimulation, J. Clin. Endocrinol. **7**:465 (June) 1947.

10. Albright, F.; Smith, P. H., and Frasier, R.: Syndrome Characterized by Primary Ovarian Insufficiency and Decreased Stature: Report of Eleven Cases with Digression on Hormonal Control of Axillary and Pubic Hair, Am. J. M. Sc. **204**:625 (Nov.) 1942.

11. Rony, H. R., and Zakon, S. J.: Effects of Androgen on the Sebaceous Glands of Human Skin, Arch. Dermat. & Syph. **48**:601 (Dec.) 1943.

12. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937.

Although Danforth stated that the general body hair, or lanugo, is not influenced by endocrine factors, it is difficult to explain the pronounced diminution of body hair in cases of panhypopituitarism and in cases of severe Addison's disease.

Although hirsutism often characterizes virilizational syndromes, such as hypertrophy of the clitoris or deepening of the voice, it is seen frequently in women who are feminine, who menstruate normally and who bear children.

In order for the factors influencing hair growth to be evaluated, the growth of hair in the male will be discussed. Addison's disease may produce sparse pubic and axillary hair. Prepuberal castration does not prevent the appearance of axillary and pubic hair. Prepubescent males with panhypopituitarism acquire little, if any, axillary or pubic hair. The adrenal cortex of man or woman, accordingly, can stimulate the development of ambosexual hair in the absence of the gonads.

The truly sexual hair of the male, represented by the beard, is influenced by gonadal androgens. This concept is supported by the absence of the beard in connection with prepuberal castration and its disappearance following postpuberal castration. Hypopituitary males have no beard, whereas men with Addison's disease do not lose their beard. Baldness is prevented by castration.[13]

It may be concluded that there are three factors concerned with hair growth: (1) a constitutional factor, representing the ability of an individual hair follicle to respond to endocrine stimuli; (2) a humoral factor, which supplies the stimulus for hair production to those follicles specifically sensitive to humoral action and, (3) local factors, such as blood supply, nerve supply and nutrition of the hair follicle.

Hirsutism has been reported in cases of encephalitis, neuritis, mumps, gonadal teratoma, mental retardation and multiple sclerosis.[14] Endocrinopathies commonly associated with hirsutism are basophilic tumors or hyperplasia of the pituitary gland (Cushing's syndrome), neoplasms or hyperplasia of the adrenal cortex (adrenogenitalism, or Cushing's syndrome), arrhenoblastoma and adrenal rest tumors of the ovary, tumors of the thymus, with secondary adrenal hyperplasia,[15] and luteomas.[16]

13. Hamilton, J. B.: Male Hormone Stimulation Is Prerequisite and Incitant in Common Baldness, J. Invest. Dermat. **5**:473 (Dec.) 1942.

14. Schwartz, J. H.: Hirsutism, Psychiatric Quart. **16**:281 (April) 1942.

15. Leyton, O.; Turnbull, H. M., and Bratton, A. B.: Primary Cancer of Thymus with Pluriglandular Disturbance, J. Path. & Bact. **34**:635 (Sept.) 1931. Horrax, G.: Further Observations on Tumor of Pineal Body, Arch. Neurol. & Psychiat. **35**:215 (Feb.) 1936.

16. Saphir, O.: So-Called Lutein Cell Tumors, Am. J. Obst. & Gynec. **37**:1008 (June) 1939. Geist, S. H., and Gaines, J. A.: Diffuse Luteinization of Ovaries Associated with Masculinization Syndrome, ibid. **43**:975 (June) 1942.

Various drugs, such as diphenylhydantoin sodium (dilantin sodium®),[17] have been reputed to cause hirsutism. Permanent or transient hirsutism may accompany the menarche, pregnancy or menopause. Heredity may be a factor in excessive hair growth. Some families, notably Jewish and Italian ones, are hirsute. The endocrine puzzle of heterosexual hirsutism was discussed in a recent editorial.[18] Bissell and Williams [1] published a detailed review of the endocrine factors of normal and abnormal hair growth.

We studied a group of patients with essential, or simple, hirsutism and contrasted them with patients having known endocrine disorders in order to determine whether there were any significant endocrinologic factors which could be correlated with this cutaneous manifestation. Patients were not selected except for comparable laboratory and clinical data. The hirsutism of the group with the essential type was severe enough to require shaving or to cause psychic disturbances, such as an inferiority complex, depression, psychoneurosis and contemplated suicide. Danforth [19] stated that approximately one third of apparently normal white women have some degree of hypertrichosis.

LABORATORY METHODS

Quantitative determinations of urinary gonadotropins and 17-ketosteroids were made.

Gonadotropins.—Gonadotropin determinations were made on four to six consecutive twenty-four hour collections of urine. Urinary extractions and bioassays were made by a method developed by one of us (A. A. S.) in the endocrinology laboratory of Duke Hospital. The procedure begins with immediate urinary dialysis, followed by complete precipitation with 95 per cent alcohol under refrigerated conditions, with the temperature lower than 10 C. After the supernatant fluid has been siphoned off, the precipitate is washed several times with acetone and ether and dried under a vacuum. An aqueous elution of the dried powder is injected subcutaneously into immature female albino rats. The assay units are based on fractional, twenty-four hour urinary aliquots, which cause a minimal increase of 100 per cent in uterine and ovarian weights over those of control rats given injections of known negative extracts. Values for normally menstruating female adults, exclusive of preovulatory wave, are as follows: 3 to 10 rat uterine units per twenty-four hours, with an average of 5 units; and 1.5 to 5 rat ovarian units per twenty-four hours, with an average of 3 units.

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17. Goodman, M. A., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941. Palmer, H. D., and DeRonde, M.: Reversible Testosterone Induced Virilism, J. Clin. Endocrinol. **3**:428 (July) 1943.

18. The Endocrine Puzzle of Heterosexual Hypertrichosis (Hirsutisi), editorial, J. Clin Endocrinol. **3**:426 (July) 1943.

19. Danforth, C. H.: Studies on Hair, with Special Reference to Hypertrichosis, Arch. Dermat. & Syph. **11**:494 (April); 637 (May); 804 (June) 1925; **12**:76 (July); 195 (Aug); 380 (Sept.); 528 (Oct.) 1925.

17-Ketosteroids.—The method used for the determination of urinary 17-ketosteroids is an adaptation by one of us (A. A. S.) of various standard procedures.[20] Fractional (one-eighth to one-fourth) twenty-four hour specimens of urine of three to four successive days are used. The method begins with acid hydrolysis of the urine under reflux, followed by extraction with carbon tetrachloride, employing a continuous extractor. The carbon tetrachloride is removed by vacuum distillation, leaving the urinary extract, a crude residue. The residue is passed through several purifications, including a procedure with the Girard reagent T. For final assay, the Zimmermann meta-dinitrobenzene color reaction is employed, according to Holtorff and Koch.[20e] A Klett-Summerson photoelectric colorimeter is used to measure color intensity. Pure crystalline androsterone is the standard. The range of values for normally menstruating adult women is 4.0 to 14.0 mg. per twenty-four hours.

The assay of urinary steroids was discussed in a recent symposium by a number of English workers, including Bishop[21] and Callow.[22] Friedgood and Whidden,[23] among others, also considered the assay of crystalline urinary androgens.

CLINICAL DATA

The data on 30 patients with idiopathic hirsutism are contrasted with those for patients with known endocrinologic disorders, including 10 with Cushing's syndrome, or adrenogenitalism, and 9 with virilizing tumors of the ovary.

The entire group was analyzed with reference to age, color, sex, marital status, whether or not pregnancy had occurred, age at menarche, ovarian cycle, libido, previous endocrine therapy, average weight and present weight and the duration of the hirsutism. Physical examination included an evaluation of the blood pressure, habitus, skin, hair distribution, degree of hirsutism, degree of obesity, thyroid function, bone age, breasts and genital organs. Laboratory studies included basal metabolic

20. (*a*) Callow, N. H.; Callow, R. V., and Emmens, C. W.: Colorimetric Determination of Substances Containing Grouping—CH_2CO—in Urine Extracts as Indication of Androgen Content, Biochem. J. **32**:1312 (Aug.) 1938. (*b*) Talbot, N. B.; Butler, A. M., and MacLachlan, E.: The Colorimetric Assay of Total, α-, and β-17-Ketosteroids in Extracts of Human Urine, J. Biol. Chem. **132**:595 (Feb.) 1940. (*c*) Cohen, R. I., and Salter, W. T.: Urinary 17-Ketosteroids in Metabolism: Standardized Chemical Estimation, ibid. **152**:489 (March) 1944. (*d*) Hershberg, E. B., and Wolfe, J. K.: A Rapid Extractor for Urinary Steroids, ibid. **133**:667 (May) 1940. (*e*) Holtorff, A. F., and Koch, F. C.: Colorimetric Estimation of 17-Ketosteroids and Their Application to Urine Extracts, ibid. **135**:377 (Sept.) 1940.

21. Bishop, P. M. F.: The Clinical Significance of Urinary Steroid Assays, J. Endocrinol. **5**:81 (Jan.) 1948.

22. Callow, R. K.: The Chemical Estimation of Urinary Neutral 17-Ketosteroids, J. Endocrinol. **5**:67 (Jan.) 1948.

23. Friedgood, H. B., and Whidden, H. L.: Assay of Crystalline and Urinary Androgens, with Special Reference to Their Measurement by Colorimetric Method, New England J. Med. **220**:736 (May 4) 1939.

tests, determination of serum cholesterol and blood glucose, glucose tolerance tests, measurements of visual fields, roentgenography of the sella turcica and determinations of urinary gonadotropins and 17-ketosteroids.

In the group of women with essential hirsutism there were 30 white female patients, 18 of whom were single and 12 married. Twelve were obese and 18 of normal weight; 24 had a gynecoid habitus and 6 an android habitus and 23 had android pubic hair and 7 gynecoid pubic hair. The clitoris was normal in all 30 patients, as were the breasts. Seven of the patients had oily skin, with some acne; 6 had dry skin, and 16, normal skin. Roentgenograms revealed a normal sella turcica for each of the 30 patients. For the 22 patients who had visual field studies, these findings were normal. Eleven patients had glucose tolerance tests, with low normal glucose tolerance curves observed in 4, and normal glucose tolerance curves in 7. The average age was 27.9, with a range from 15 to 43. The average menarcheal age was 13, with a range from 11 to 17. In 23 patients the menstrual flow was normal, in 5 the flow was short, and 2 had prolonged ovarian cycles. The average weight was 147 pounds (67 Kg.), with a range from 85 to 250 pounds (39 to 113 Kg.). The weight at the time of examination averaged 154.2 pounds (70 Kg.), with a range from 85 to 263 pounds (39 to 119 Kg.). The average duration of the hirsutism was 6.43 years, with a range from one to fifteen years. The average blood pressure was 124 systolic and 76 diastolic, with a range from 100 systolic and 60 diastolic to 155 systolic and 90 diastolic. The basal metabolic rate averaged — 4 per cent, with a range from — 14 to — 15. Urinary gonadotropins averaged 5.5 rat uterine units per twenty-four hours, with a range from 2 to 10 units, and 3.7 rat ovarian units, with a range from 2 to 8 units. Urinary 17-ketosteroids averaged 10.6 mg. per twenty-four hours, with a range from 5.4 to 20.3 mg.

Ten patients with Cushing's syndrome, or adrenogenitalism, were studied. All were white women, 7 of whom were married and 3 single. The average age was 35, with a range from 26 to 43. The average menarcheal age was 13 years 9 months, with a range from 11 to 24. Two patients had had amenorrhea for one year; 1 for four years, and 1 for fourteen years. The remaining patients had infrequent menstrual cycles, with usually scanty flow. The average weight was 184 pounds (83 Kg.), with a range from 100 to 300 pounds (45 to 136 Kg.). The average weight at examination was 196 pounds (89 Kg.), with a range from 137 to 325 pounds (62 to 147 Kg.). The average duration of the hirsutism was eight years nine months, with a range from two to twelve years. The average blood pressure was 156 systolic and 100 diastolic, with a range from 200 systolic and 100 diastolic to 116 systolic

and 78 diastolic. The habitus of all was android. The hair distribution was android in 9 patients and gynecoid in 1 patient. Nine of the 10 persons were obese; 9 had normal breasts, and 1 had small breasts. The clitoris was normal in all. The skin in 8 was normal, and in 2 it was oily, with an acneform eruption. The basal metabolic rates averaged — 4 per cent, with a range from — 17 to + 26 per cent. Serum cholesterol values averaged 200 mg. per hundred cubic centimeters, with a range from 160 to 270 mg. Blood glucose values averaged 138.5 mg. per hundred cubic centimeters, with a range from 80 to 218 mg. Glucose tolerance tests yielded diabetic curves for 5 patients and normal curves for 5 patients. Visual fields and roentgenograms of the sella turcica were normal in all patients. The output of urinary gonadotropins averaged 8 rat uterine units per twenty-four hours, with a range from 2 to 14 units, and 3.75 rat ovarian units per twenty-four hours, with a range from 2 to 6 units. Urinary 17-ketosteroids averaged 13.25 mg. per twenty-four hours, with a range from 6 to 26.3 mg.

All the 9 patients with masculinizing tumors of the ovaries were white. The average age was 29.4, with a range from 22 to 44. The average menarcheal age was 12, with a range from 11 to 14. One patient had had amenorrhea for fifteen months, 1 for eighteen months, 1 for twenty-four months and 1 for thirty-six months. The rest of the patients had infrequent cycles and usually scanty flow. The average weight was 141 pounds (64 Kg.), with a range from 120 to 180 pounds (54 to 81 Kg.). The average weight at examination was 148 pounds (67 Kg.), with a range from 120 to 199 pounds (54 to 90 Kg.). The hirsutism had been present for an average duration of five years nine months, with a range from two to twelve years. The blood pressure averaged 125 systolic and 84 diastolic, with a range from 140 systolic and 100 diastolic to 116 systolic and 60 diastolic. Five were of android habitus, and 4, of gynecoid habitus. The hair distribution in all was android. Four of the 9 were obese; all 9 had normal breasts; 5 had a large clitoris, and 4 had a normal clitoris. Five had oily, acneform skin, and 4, normal skin. The basal metabolic rate averaged — 3 per cent, with a range from — 26 to + 19 per cent. The serum cholesterol averaged 195 mg. per hundred cubic centimeters, with a range from 170 to 230 mg. The blood glucose averaged 98 mg. per hundred cubic centimeters, with a range from 84 to 108. Glucose tolerance tests for 8 of the patients gave normal curves. The visual fields and roentgenograms of the sella turcica were normal in all 9. Urinary gonadotropins averaged 7.5 rat uterine units per twenty-four hours, with a range from 2 to 24 units, and 5 rat ovarian units per twenty-four hours, with a range from 2 to 16 units. Urinary 17-ketosteroids averaged 18.7 mg., with a range from 3.1 to 49.7 mg.

COMMENT

These data emphasize commonly held impressions, namely, that the intensity, amount and distribution of hirsutism are not diagnostic evidence of endocrinopathy. On the other hand, patients with established virilizing syndromes may have unimpressive hirsutism. These facts emphasize that patients with hirsutism warrant capable medical consideration. By no means, however, is it necessary that they undergo complicated special endocrinologic studies.

If a woman with hirsutism has cyclic uterine bleeding of normal duration and has no symptoms or signs of virilization, it is unlikely that there is any endocrine cause for her hirsutism. If it can be proved, by basal temperature graphs or by endometrial biopsy, that this patient has normal ovulatory function, it becomes practically certain that no endocrine disease exists, since normal ovarian function is not compatible with the virilizational syndromes.

The symptom complex of gravest prognosis is amenorrhea and hirsutism. By amenorrhea we mean an abscence of uterine bleeding for twelve months or longer.

In conjunction with hirsutism, progressively less frequent and progressively scantier flow warrant definitive studies. The basal temperature curves or endometrial biopsy data may confirm or negate the presence of qualitative failure in ovarian function, which may be related to endocrinopathic hirsutism.

Other symptoms which have diagnostic and prognostic weight when conjoined with hirsutism include obesity, coarsening of the voice, psychosexual alterations and alterations in libido.

The chief basis for the differentiation of essential hirsutism and hirsutism associated with endocrine disease lies in the clinical approach rather than in laboratory investigations. A careful consideration of the patient's symptoms along the lines which have been discussed and a general physical examination, including a gynecologic study, should be ample for the screening of most patients. Special studies which are of value, and which have been mentioned, include determinations of basal temperature curves and studies of endometrial biopsy specimens.

Methods of hormonal quantitation which are adaptable to clinical practice yield a paucity of data in the differentiation of idiopathic hirsutism and endocrinopathic disease associated with hirsutism. Commonly employed, but not infrequently misunderstood, are values for the urinary 17-ketosteroids. A few statements about the significance of these substances seem justified. In the female, the 17-ketosteroids represent normal degradational products of the metabolism of androgens and androgen-like substances of the adrenal cortex. The urine of the normal female contains four of these adrenal 17-ketosteroids: isoandrosterone,

dehydroisoandrosterone, androsterone and etiocholane-3α-ol-17-one. Although these four products are derivatives of androgens, they vary in their true androgenism. The most active is androsterone; the next most active, dehydroisoandrosterone, and the next after that, isoandrosterone. Etiocholane-3α-ol-17-one is biologically inactive.

Urinary 17-ketosteroids are reported in terms of milligrams excreted per twenty-four hours. The milligram unit has no biologic equation; it is determined colorimetrically. It is possible for the androgenicity of samples of urine yielding the same values for 17-ketosteroids to vary 1,000 per cent or more.

The determination of alpha and beta urinary 17-ketosteroids, a procedure which is not particularly difficult, does not aid materially in verifying the presence or absence of increases in 17-ketosteroids of high androgenicity or of low androgenicity.

Urinary 17-ketosteroids and urinary androgens, therefore, cannot be considered the same. If it were possible to quantitate urinary androgens as a clinical procedure and simultaneously to compare these results with those for urinary estrogens, the androgen-estrogen ratio of a patient could be established. Such a ratio would express the degree of androgenicity and the degree of estrogenicity of the patient. These data might well prove helpful in the evaluation and study of patients with idiopathic hirsutism. Such determinations are not practical with present methods of hormone study.

The determination of the androgen-estrogen ratio is not necessary to establish a diagnosis of endocrinopathic hirsutism. Ordinary, careful clinical investigations can do this. These data, however, may elucidate the problem of essential hirsutism. They may confirm or negate various theories which have been propounded as to the etiology of the condition, including those of relative or borderline hyperplasia of the adrenal cortex and of incomplete differentiation of the female gonad, with a preponderance of medullary structures remaining unsuppressed.

The 30 women with essential hirsutism who have been studied gave no evidence of ovarian failure, in direct contrast to the patients presented with proved endocrinopathies. Some of these women—to be specific, one third—had prolonged ovarian cycles, with a maximum duration of sixty days, but all had flows of normal amount and duration. These not uncommon variations in cycle length were not associated with any evidence of endocrine disease. Furthermore, they were not associated with any significant alterations in urinary 17-ketosteroids. For the 5 patients who had 17-ketosteroid values above the upper range of what is considered normal, the average cycle length was forty-four days, with a range from twenty-eight to sixty days.

Whatever the cause of essential hirsutism is, by definition, it is not known. Accordingly, there is no specific treatment for the condition.

Parenthetically, excess hair falls slowly, even when specific treatment of endocrinopathic hirsutism is observed. In fact, except for coarsening of the voice and hypertrophy of the clitoris, hirsutism often constitutes the most persisting stigma of a virilizing syndrome after the virilizing tumor has been removed and there has been a return of normal ovarian function. In view of these facts, it seems a rather ambitious hope to expect estrogen therapy to cause excessive hair to fall in essential hirsutism. It seems to make little difference whether the estrogens are given orally or intramuscularly or are rubbed into the skin as ointments. The empiric use of estrogens in treatment of patients with essential hirsutism and, by inference, with normal ovarian function not only may fail to relieve the hirsutism but also may bring about significant alterations in ovarian function. The ovarian cycle, with both its qualitative and its quantitative values, may be disturbed and various irregularities of uterine bleeding precipitated. Furthermore, local gynecologic disease, such as carcinoma or endometriosis, undiagnosed and unsuspected by those who practice empiricism, may be aggravated.

The only therapeutic recommendations which can be given the patient with essential hirsutism are either that the patient forget and ignore the condition or that various palliative treatments, including shaving, manual epilation, bleaching and/or electrolysis, be tried.

SUMMARY

The dermatologic and endocrinologic factors in normal and abnormal hair growth are discussed.

The clinical and laboratory data concerning 30 patients with essential hirsutism and for 19 patients with endocrine disease associated with hirsutism are analyzed.

Hirsutism warrants medical investigation. Essential and endocrinopathic hirsutism may be differentiated by ordinary clinical investigations. Special hormonal studies are of relatively little value in the differentiation.

There is no specific endocrine treatment for essential hirsutism.

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ABSTRACT OF DISCUSSION

DR. HERBERT RATTNER, Chicago: Hirsutism, despite its common occurrence, remains one of the obscure and unsolved problems of medicine. As Dr. Callaway and his associates indicated, it is a problem that sometimes assumes proportions of great importance. It may be noted that among their patients there were some with psychoneuroses severe enough to cause them to contemplate suicide. Hirsutism is an abnormal condition difficult to explain because even the control of normal hair growth is obscure and unexplained. Hair growth is a complex mechanism influenced, apparently, by constitutional, endocrinologic, genetic and racial factors, and perhaps by local factors, such as follicular nutrition, blood

supply and nerve supply. Of these, the endocrinologic factor has long been considered one of the more important influences. The literature contains ample experimental and clinical evidence to suggest a strong link between the function of the various endocrine glands and hirsutism. Unfortunately, the experimental evidence is not always applicable to man, whose hairy system is unique and complicated, and while hirsutism has been reported in many pathologic entities involving endocrine glands, on occasion women with virilizing syndromes may have but little hirsutism, while others with abundant hair growth may exhibit no evidence of endocrine abnormalities. In an attempt to solve this particular puzzle, Dr. Callaway and his co-workers have studied two groups of patients with the hope of finding a common denominator that would serve as a clue to the mystery of hirsutism. Unfortunately, no such factor was found. Studies were conducted both clinically and in the laboratory, with special emphasis on endocrine factors. Of all the technics employed, it was found that the clinical investigations proved to be most significant, that clinical investigations alone were sufficient to differentiate idiopathic hirsutism from the endocrinopathic variety and that special hormonal studies were of little value. It is stated specifically that the chief reliance for the differentiation of the two varieties of hirsutism lies in the clinical approach rather than in laboratory investigations and that it is unnecessary to institute complicated special endocrinologic studies. I should like to amend this view somewhat by repeating the advice offered us at Michael Reese Hospital by Dr. Rachmael Levine, the endocrinologist. He advocated what he called a whole approach, without the limiting of investigations to necessary technics only. In all medical problems that are not fully understood it is desirable to attack from all sides, to undertake complete clinical and laboratory studies in a large number of cases, if possible, even though it may be anticipated that these studies may furnish no information of value. Indeed, dermatologists might well heed the example of the oncologists, who are studying their problem from all angles with the hope that one of their studies may lead to a solution. Laboratory and clinical methods complement each other. Accordingly, in the investigation of a case of permanent hirsutism, the minimum procedures for endocrinologic studies should consist of determinations of basal body temperature; study of vaginal smears in the first half of the menstrual cycle and a pregnandiol test in the second half to determine the status of estrogen and corpus luteum, respectively, and the measurement of urinary 17-ketosteroids. These highly desirable and pertinent procedures are neither expensive to the patient nor too complicated to be carried out in a well conducted laboratory. Only by means of such routine studies in a large number of cases might one conceivably uncover a steroid abnormality or some other change of significance.

The authors' conclusions are correct. Clinical investigations are of greatest importance; hormonal studies most often offer little of value in solution of the problem of idiopathic hirsutism; there is no specific endocrinologic treatment for the condition, and empiric treatment with endocrinal substances is to be decried.

Nevertheless, the subject is of such importance and the problem so complex that similar studies should be encouraged and carried further. Knowledge of the endocrine glands is developing constantly. Perhaps newer knowledge of steroid chemistry will disclose the cause of hirsutism. I hope that Dr. Callaway and his associates will continue with their study and that they will continue to complement their clinical studies with laboratory investigations. The subject is an important one, if only because the condition causes distress to such large numbers of women. This paper by Dr. Callaway and his co-workers should stimulate dermatologists to further study.

DR. GROSVENOR W. BISSELL, Chicago: In the cases of idiopathic hirsutism my associates and I have studied, clinical observations and chemical and endocrinologic studies have been similar to those reported. In our experience, overweight seems to have been more commonly observed, however, and it has been our observation that this increase in body weight frequently followed the appearance of the abnormal facial hair. Since the relation of obesity to psychogenic disturbances is now well recognized, we have wondered whether the increase in weight is not a reflection of the patient's psychiatric reaction to the appearance of the hirsutism rather than the result of any more specific metabolic cause. We have likewise found a lessened carbohydrate tolerance in a large percentage of our patients, but this, again, may be predicated on the greater occurrence of obesity in our group, since many obese persons have abnormal glucose tolerance curves which revert to normal if normal weight is resumed.

I should like to reemphasize Dr. Callaway's appeal for a pertinent clinical approach to the subject of hirsutism. The absence of accompanying signs of virilism is an important clinical confirmation that one is dealing with the idiopathic variety of hirsutism. Dr. Callaway's use of determinations of basal body temperatures and of biopsies of endometrial tissue to establish the presence of ovulatory cycles seems to us to be a particularly valuable adjunct in the recognition of idiopathic hirsutism, especially in cases in which there are accompanying menstrual irregularities.

The racial and familial genetic history of the patient must likewise be carefully appraised.

I should like to mention the occurrence of a transient, self-limited type of idiopathic hirsutism which is occasionally observed. This type of hirsutism is sometimes seen during the course of pregnancy and may persist until after delivery or disappear even before delivery has taken place. A family history of the occurrence may sometimes be elicited. My associates and I have likewise seen transient hirsutism follow severe thermal burns. It has been reported also sometimes to accompany states of extreme starvation.

We are in complete agreement with Dr. Callaway with regard to the treatment of idiopathic hirsutism. No specific therapy is presently available, and, although local therapy of the condition is not particularly successful, this form of treatment, together with psychotherapy and reassurance, is the only one that we feel is justified at present.

It is obvious from what has been presented that this condition of unknown etiology needs much more intensive investigation. The frequent occurrence of the abnormality among certain families and racial groups would seem to indicate that part of the problem must await solution by the geneticist.

Although a specific endocrine cause of this disorder is not presently demonstrable, there are certain leads which suggest that the development of better technics may result in the demonstration of a causal endocrine relation. Dr. Callaway has mentioned the desirability of determining androgen-estrogen ratios for these patients. Glass and Bergman have performed such a study on a small group of idiopathically hirsute women and have demonstrated that the ratio of androgens to estrogens was greater in these subjects than in normal women.

Idiopathic hirsutism frequently makes its appearance at the time of the menarche, pregnancy or the menopause. It may transiently accompany severe thermal burns or pronounced states of inanition. All these events are associated with altered function of the adrenal cortex. It would seem, then, that although present assay methods do not demonstrate clearly such a connection, this disorder may have at least a component of adrenal malfunction. There is also recent evidence

by Albright that the adrenal response to stress in idiopathically hirsute women is greater than in the normal woman and more closely resembles that of the normal man.

Dr. Callaway has pointed out the disparity between the 17-ketosteroid assay and fractionated androgen assays on the same subject. I should like further to point out that these are both tests of the end results of any given person's steroid metabolism; an accurate estimation of their individual significance or their relation to each other must await clarification of the intermediary metabolism involved, about which virtually no data exist.

Obviously, a final answer to this problem will come only when there has been more intensive study of the disorder. I congratulate Dr. Callaway and his associates on their paper, which represents a valuable and needed contribution to the clarification of this difficult condition.

Dr. John H. Lamb, Oklahoma City: At the annual meeting of the Association for the Study of Internal Secretions, on June 18, 1948, Dr. Roney presented an interesting and stimulating paper on pseudoglandular disturbance which may throw light on the problem of essential hirsutism. He stated that, in general, hormonal effects depend on end organ sensitiveness, as well as on the active hormone, and that normal levels of the stimulating hormone may invoke a greater intensity of response because of this increased end organ sensitivity. He included essential hirsutism in this category. I wish to point out that about forty-two other steroids have now been isolated from normal and pathologic urine. It is a possibility that future investigations may relate one of these new steroids to specific conditions, such as the stimulation of excessive hair growth in women.

Dr. Maurice Oppenheim, Chicago: About thirty years ago, in the department of dermatology in the Wilhelminen Hospital, Vienna, injections of argyrol,® (a preparation of silver with a protein produced by the electrolysis of serum albumin), strong protein silver N. F. (protargol®) and silver nitrate in various concentrations were given to infants and babies infected with gonorrhea, and the treatment was continued for a long time: two months, three months and six months. Then my associates and I made the normal irritation and stimulation tests to find out whether the babies and infants were free from gonococci. At that time there was no treatment with estrogen or with penicillin, but only the local treatments were possible.

In the course of this treatment, we saw, in some of these subjects, hair growing on the labia majora, on the anus and on the pubes. There were no lanugo hairs, but bristle and long hairs, not many.

We concluded that as a consequence of this treatment the hair growth was produced. We had no explanation for this.

Later we found that most of those children who showed the hair growth started to masturbate. So sexual development was stimulated by this treatment. We used only local treatment at the time. No external irritation was visible; the other children did not show this hair growth. There were no black-stained preexisting hairs which had been overlooked. We came to the conclusion that the repeated local treatment of the genital area was in some way stimulating the ovarian function to produce more hormones, so that the hair growth was initiated. This is only a small experimental contribution to this question. I am sorry that I cannot present the slides which I made many years ago. But it is evident that by local irritation of the genitals, vulva, urethra and vagina one can produce, in some persons, an abnormal hair growth on the pubic and genital area.

DR. J. LAMAR CALLAWAY, Durham, N. C.: I should like to say again, as I did in the paper, that many of our studies were patterned after those of Drs. Bissell and Williams. Our findings were somewhat similar to theirs.

Dr. Bissell called attention to the transient hirsutism that sometimes occurs at the menarche, during pregnancy and at the menopause. This needs no specific treatment.

Dr. Rattner was correct in indicating that all patients with hirsutism should have a complete clinical and laboratory evaluation. I should like to emphasize that laboratory findings should be evaluated very critically, however.

Dr. Lamb pointed out, as did Dr. Bissell, that newer and more accurate clinical and laboratory methods for evaluating ketosteroid determinations are now beginning to be developed. Perhaps physicians will be in a position soon to make androgen determinations.

I was much interested in Dr. Oppenheim's report of pubic and genital hair growth as a result of local irritation from the preparations which he used. This observation may possibly have some significance in connection with facial hirsutism.

TREATMENT OF NEUROSYPHILIS WITH PENICILLIN COMBINED WITH ARTIFICIAL FEVER

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THE VALUE of penicillin as a therapeutic agent in neurosyphilis is well established. The exact degree to which it may be relied on to prevent the development of neurosyphilis or to repair pathologic processes produced by Treponema pallidum in the central nervous system has not been determined. Since the introduction of penicillin as an antisyphilitic remedy by Mahoney [1] in 1943, much research work has been done in the field of neurosyphilis. The early optimism expressed by these workers appears to be justified.

The papers of Stokes,[2] Moore,[3] Rose,[4] Callaway,[5] Koteen,[6] Curtis,[7] O'Leary [8] and their associates amply confirm the fact that penicillin

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From the Department of Dermatology of the Division of Medicine of the University of California Medical School and the Department of Dermatology of the Mount Zion Hospital.

1. Mahoney, J. F.; Arnold, R. C., and Harris, A. D.: Penicillin Treatment of Early Syphilis, Ven. Dis. Inform. **24**:355-357 (Dec.) 1943.

2. (*a*) Stokes, J. H., and others: The Action of Penicillin in Late Syphilis, Including Neurosyphilis, Benign Late Syphilis and Late Congenital Syphilis: Preliminary Report, J. A. M. A. **126**:73-79 (Sept. 9) 1944. (*b*) Gammon, G. D., and others: Penicillin in Neurosyphilis: Effect on Blood and Spinal Fluid, ibid. **128**:653-654 (June 3) 1945. (*c*) Stokes, J. H.; Boerner, F.; Hitchens, A. P., and Nemser, S.: Penicillin Alone in Neurosyphilis, ibid. **131**:1-7 (May 4) 1946. (*d*) Stokes, J. H.; Steiger, H. P., and Gammon, G. D.: Three Years of Penicillin Alone in Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **32**:28-42 (Jan.) 1948.

3. Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: Penicillin in the Treatment of Neurosyphilis: II. Dementia Paralytica, J. A. M. A. **131**:1255-1260 (Aug. 17) 1946. Moore, J. E., and Mohr, C. F.: Penicillin in the Treatment of Neurosyphilis: Asymptomatic Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **30**:405-419 (Sept.) 1946.

4. Rose, A. S., and others: The Penicillin Treatment of Neurosyphilis: Preliminary Report of Seventy Cases Followed from Four to Twelve Months, Am. J. Syph., Gonor. & Ven. Dis. **29**:487-493 (Sept.) 1945. Rose, A. S., and Solomon, H. C.: Penicillin in Treatment of Neurosyphilis: Study of One Hundred Cases Followed Twelve Months or More, J. A. M. A. **133**:5-10 (Jan. 4) 1947.

(Footnotes continued on next page)

has a profound beneficial effect on the abnormalities of the spinal fluid and the clinical course of neurosyphilis. All these papers are clinical, and, except for the reports of Rose [4] and Curtis,[7] the use of penicillin alone as the therapeutic agent is stressed. The latter authors discuss the therapeutic effects of penicillin alone as well as of penicillin combined with fever therapy.

A recent publication on this subject is that of Stokes and associates.[2d] These authors reported the effects of the use of penicillin alone in treatment of 361 patients with neurosyphilis who were observed for 90 to 1,100 days. Their findings indicate that in its effects treatment with penicillin alone is at least equal to a combination of fever therapy and chemotherapy and is superior in dealing with some forms of neurosyphilis. The authors stated the conclusion that penicillin seems to be more effective in controlling the mechanism which produces abnormalities in the spinal fluid than in controlling that which causes the symptoms of neurosyphilis. On the other hand, malarial or fever therapy affects the symptom-producing mechanism more than it does that which leads to spinal fluid abnormalities. These authors expressed the opinion, as have others, that a combination of fever therapy and treatment with penicillin may give a prompter result than does either alone.

COMBINATION OF PENICILLIN WITH FEVER THERAPY

Previous to the introduction of penicillin, fever therapy had been established as the procedure of choice for the treatment of various forms of symptomatic neurosyphilis and resistant asymptomatic neurosyphilis.

Eagle [9] recently showed that in vitro the spirocheticidal property of penicillin is enhanced by elevation of the temperature of the testing solution. In a solution of penicillin containing 25 to 250 units per cubic centimeter he found that the following conditions exist:

At 8 C. all the T. pallidum remain viable for twenty-four hours.

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5. Callaway, J. L., and others: The Use of Penicillin in the Treatment of Syphilis of the Central Nervous System: Report of One Hundred Patients, Am. J. Syph., Gonor. & Ven. Dis. **30**:110-124 (March) 1946.

6. Koteen, H.; Doty, E. J.; Webster, B., and McDermott, W.: Penicillin Therapy in Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:1-13 (Jan.) 1947.

7. Curtis, A. C.: Neurosyphilis: Treatment with Penicillin Alone and with a Combination of Penicillin and Malaria, read before the Thirteenth Venereal Disease Control Seminar, United States Public Health Service, San Francisco, Calif., May 26, 1947.

8. O'Leary, P. A.; Brunsting, L. A., and Ockuly, O.: Penicillin in the Treatment of Neurosyphilis, J. A. M. A. **130**:698-700 (March 16) 1946.

9. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Effect of Hyperpyrexia on the Therapeutic Efficacy of Penicillin in Experimental Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:239-245 (May) 1947.

At 22 to 23 C. 10 per cent of the T. pallidum remain viable for twenty-four hours.

At 32 to 33 C. 1 per cent of the organisms remain viable for twenty-four hours.

At 39 to 40 C. only 0.02 per cent of the organisms remain viable for twenty-four hours.

It should be pointed out that temperatures of 39 and 40 C. are lethal to T. pallidum. This does not vitiate the fact that Eagle's experiments show a definite increase in the spirocheticidal effect of penicillin in vitro under conditions of increased temperature of the testing solutions.

Eagle further showed that the curative dose of penicillin in rabbit syphilis is reduced eight to ten times by the elevation of the animal's temperature 3 to 4 F. over a ten-hour period during the administration of the pencillin. This work indicates that the favorable effect of fever on penicillin therapy is accomplished probably by (1) its enhancing the therapeutic efficacy of the penicillin and (2) a synergistic or additive effect.

Eagle,[10] as well as Boak,[11] Carpenter[12] and their co-workers, showed that T. pallidum becomes more vulnerable to water-soluble bismuth compounds, neoarsphenamine and oxophenarsine hydrochloride (mapharsen®) when exposed to these drugs under conditions of increased temperature.

When one considers the aforementioned experimental findings and the definite beneficial effects of artificial fever on the clinical course of neurosyphilis, it appears logical that a combination of penicillin and fever therapy should produce better effects than either procedure alone. Moore[3] recommended the combined use of penicillin and fever for certain forms of neurosyphilis. Rose[4] stated the opinion that the administration of penicillin alone has not proved as effective as has treatment with penicillin and fever. Curtis[7] expressed the belief that the administration of penicillin was somewhat more effective when combined with fever therapy than when used alone. Later, at the meeting of the American Academy of Dermatology and Syphilology in December 1947, he stated the conclusion that penicillin was as effective in the treatment of neurosyphilis when used alone as when combined

10. Eagle, H.: The Minimal Effective Concentrations of Arsenic and Bismuth Compounds on T. Pallidum in Vitro in Relation to the Therapeutic Dose, Am. J. Syph., Gonor. & Ven. Dis. **23**:310-318 (May) 1939.

11. Boak, R. A.; Carpenter, C. M., and Warren, S. L.: The Concurrent Treatment with Fever and Neoarsphenamine of Experimental Syphilis in Rabbits, Am. J. Syph., Gonor. & Ven. Dis. **26**:282-290 (May) 1942.

12. Carpenter, C. M.; Boak, R. A., and Dorn, F. S.: The Concurrent Treatment of Experimental Syphilis with Fever and Mapharsen, Am. J. Syph., Gonor. & Ven. Dis. **31**:498-505 (Sept.) 1947.

with fever therapy. O'Leary,[8] in a small number of cases of neurosyphilis, noted no increased effect when the administration of penicillin was combined with fever therapy.

PLAN OF STUDY

In this paper we wish to report on our experience with the combined use of penicillin and artificial fever in the treatment of neurosyphilis. This work began in March 1945 and was continuing at the time of writing. Until July 1946 penicillin sodium in aqueous solution, 40,000 units every three hours, administered intramuscularly, was given for fourteen to fifteen days. The treatment was begun with a dosage of 10,000 units every three hours for twelve hours, and then 20,000 units every three hours for twenty-four hours, after which time it was continued for fifteen days at the full dosage of 40,000 units. A total dosage of 4,000,000 to 4,500,000 units was administered. While the patient was hospitalized he was given fever therapy, consisting of the induction of temperatures of 40 to 40.5 C. (104 to 105 F.) for five hours, twice weekly. The fever was induced by means of the blanket method, a simple mechanical means described by one of us (N. N. E.) in 1937.[13] Each patient received, as a rule, four fever treatments during his two weeks of hospitalization. These were followed by a weekly fever treatment until a total of ten to fifty hours of fever had been given.

Since July 1946 a majority of the patients have been given 300,000 units of penicillin calcium suspended in peanut oil containing 4.5 per cent white wax U. S. P. (the Romansky formula) intramuscularly, once daily for twenty days, or a total of 6,000,000 units. Fever therapy as previously described was administered weekly during and subsequent to the penicillin therapy until ten fever treatments had been given. This ambulatory method of penicillin therapy facilitated the work as it lessened the expense and eliminated the two week hospitalization period. The patient was hospitalized for twenty-four hours during each fever treatment.

Follow-up observations consisted of repeated clinical and laboratory examinations at intervals of from four to six months. Additional treatment was given whenever the clinical or serologic response did not appear satisfactory.

CLINICAL MATERIAL

A total of 87 patients with various forms of neurosyphilis were treated with penicillin as well as artificial fever. Of this group 55 patients have been followed for one hundred and twenty days or longer, and sufficient data as to their clinical and serologic progress are available

13. Epstein, N. N.: The Blanket Method of Inducing Artificial Fever, Arch. Phys. Therapy **18**:199-205 (April) 1937.

for presentation in this report. The entire group of 87 patients, however, will be discussed from the standpoint of reactions to treatment.

Twenty-eight patients received penicillin sodium in aqueous solution, together with fever therapy; 20 received penicillin in oil and wax, and 7 received at least one course of each type of penicillin, together with fever therapy. Table 1 shows the clinical diagnoses for the entire group of 55 patients.

CLINICAL RESPONSE

The number of patients in each of the diagnostic categories was too small for statistical analysis of the clinical effects which were produced by the treatment. The group with dementia paralytica was the largest, and some conclusions can be drawn concerning the efficacy of the combination of penicillin and fever therapy in these patients. No striking effects were noted in the group with tabes dorsalis.

Of the 25 patients with dementia paralytica, 8 showed pronounced clinical improvement; 10, moderate improvement; 2, slight improvement, and 5, no change. The patients with early dementia paralytica responded best; 1 patient with acute symptoms had remarkable clearing, and 2 with advanced, appreciable deterioration did well clinically, considering the degree of mental deterioration which was present prior to the institution of treatment.

TABLE 1.—*Patients with Neurosyphilis Treated with Penicillin and Artificial Fever*

	Asymptomatic Neurosyphilis	Dementia Paralytica and Its Tabetic Form	Tabes Dorsalis	Diffuse Neurosyphilis	Meningovascular Neurosyphilis	Hereditary Neurosyphilis
Number of patients.....	16	25	4	3	3	4

In the 4 patients with optic atrophy, the vision remained stationary in 3 and was slightly decreased in 1.

The clinical response of patients with neurosyphilis to a given method of treatment is very difficult to evaluate, particularly in cases of persons with dementia paralytica. Often the subjective symptoms are vague, and changes in these symptoms may be influenced by suggestion. A large majority of these patients experienced a definite improvement in general well-being. In the group with dementia paralytica, a decrease in nervousness, indecisiveness and uncertainty was noted. Whenever there were clearcut symptoms, such as decided emotional instability, confusion and loss of memory, the treatment frequently gave noticeable relief. The pains of tabes were not noticeably benefited.

In the few patients with meningovascular syphilis, changes in objective and subjective symptoms were readily observed. In 1 patient, diplopia due to a right-sided oculomotor paralysis cleared within ten days after treatment was instituted; another patient with excruciatingly severe pains in the head obtained complete relief in five days; the third patient, who had meningovascular neurosyphilitic paresis of the left lower limb and motor aphasia, responded within a few months.

It was our impression that the patients with objective and subjective symptoms of neurosyphilis responded more promptly to penicillin and fever therapy than patients treated in the past had responded to chemotherapy combined with artificial fever therapy.

In most instances the clinical response paralleled the changes in the spinal fluid. Changes in spinal fluid probably reflect the effect of the treatment more accurately than can clinical observation.

TABLE 2.—*Changes in Patterns of the Spinal Fluid*

Grade	Before Treatment	120 to 365 Days After Treatment	365 Days + After Treatment
1	6 (11.1%)	20 (37.0%)	8 (34.4%)
2	17 (31.5%)	24 (44.4%)	2 (8.6%)
3	31 (57.4%)	5 (9.3%)	4 (17.2%)
Normal	0	5 (9.3%)	9 (38.7%)
Total	54	54	23

CHANGES IN THE SPINAL FLUID

The spinal fluid abnormalities will be considered from two standpoints, namely (1) the general pattern of the spinal fluid and (2) the individual constituents and reactions of the spinal fluids, i. e., the cell count, the protein content, the colloidal gold reaction and the Wassermann reaction. Moore's [14] classification of spinal fluid pattern or formulas was used to designate the degree of abnormality present. Grade 1 refers to minimal changes; grade 2 to changes slightly more abnormal than those of grade 1, and grade 3, to a distinctly abnormal fluid, i. e., one with the "paretic" formula.

PATTERNS OF THE SPINAL FLUID

Table 2 shows the distribution of spinal fluid patterns before and after treatment. It can be seen that the percentage of patients with grade 3 spinal fluids is appreciably decreased by treatment, i. e., from 57.4 per cent to 9.3 per cent within one year after treatment. Simul-

14. Moore, J. E.; Kemp, J. E., and others: The Modern Treatment of Syphilis, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1941.

taneously the percentage of patients with inactive spinal fluids (grades 1 and 2) increased during the first year of observation, i. e., from 42.6 per cent to 90.7 per cent. During the second year of observation (of only 23 cases) 82.8 per cent of the patients had inactive spinal fluids. Another interesting finding was the increase in the number of normal spinal fluids after treatment. Before treatment none of the patients had normal fluids; within one year after treatment 5 (of 53 patients), or 9.3 per cent, had normal fluids, and during the second year of observation 9 (of 23 patients), or 38.7 per cent, had completely normal

TABLE 3.—*Changes in Grades of Patterns of Spinal Fluid*

Grade to Grade	120 to 365 Days After Treatment	365 Days + After Treatment
3 to 3	4	3
3 to 2	15	3
3 to 1	11	6
3 to 0	0	5
2 to 2	9	0
2 to 1	6	2
2 to 0	2	3
1 to 1	3	0
1 to 0	3	1
Total	53	23

TABLE 4.—*Degree of Change in Spinal Fluid Findings*

Period of Observation	No Change	Improved	Improved Decidedly	Became Worse	Total No. of Patients
120 to 365 days	16 (30.1%)	6 (11.3%)	31 (58.6%)	0	53
365 days +	3 (13.0%)	2 (8.7%)	18 (78.3%)	0	23

spinal fluids. This observation supports the findings of others that improvement in spinal fluid abnormalities, once obtained, tends to persist and to increase. There were instances in which the spinal fluid abnormalities increased after a temporary improvement.

Tables 2 and 3 show the changes in the spinal fluid patterns. Of the group of patients who had grade 3 spinal fluids before treatment was instituted, 5 continued to show a grade 3 pattern during the first year of observation and 4 still had this pattern during the second year of observation, in spite of repeated courses of treatment. There were no significant differences in therapeutic effects noted between the group which received aqueous penicillin sodium and the one which received penicillin in oil and wax. Table 4 shows the observations of over-all changes in the spinal fluid.

CHANGES IN CELL COUNT

The cell count in the spinal fluid was distinctly influenced by the administration of penicillin combined with artificial fever therapy. In a large majority of instances the cell count returned to normal during the first year of observation. This change was usually noted after the first follow-up examination, i. e., one hundred and twenty days after the treatment had been given. The abnormal cell counts varied from 8 to 265 cells per cubic millimeter. Patients with high cell counts responded as promptly as did those with lower counts.

TABLE 5.—*Changes in Cell Count*

Abnormal Before Treatment	Period of Observation	Decreased to Normal	Decreased	Increased	No Change
32	120 to 365 days	28 (87.6%)	2 (6.2%)	2 (6.2%)	0
13	365 days +	11 (84.6%)	2 (15.4%)	0	0

TABLE 6.—*Changes in Colloidal Gold Curve*

Grade of Abnormality	No. of Cases Before Treatment	No. of Cases 120 to 365 Days After Treatment	No. of Cases 365 + Days After Treatment
1 (slight)	5	9 (20.8%)	2 (13.2%)
2 (moderate)	10	12 (27.6%)	1 (6.6%)
3 (appreciable)	28	4 (9.2%)	3 (19.8%)
Normal	0	18 (42.4%)	9 (60.4%)

TABLE 7.—*Change in Grade 3 Colloidal Gold Curves*

No. of Patients with Grade 3 Curves Before Treatment		No. Reversed to Normal	No. Reversed to Near Normal	Total Improved
28	First year of observation	11 (38.5%)	5 (17.5%)	16 (56.0%)
13	Second year of observation	9 (69.0%)	1 (7.7%)	10 (76.7%)

CHANGES IN PROTEIN CONTENT

The protein content of the spinal fluid was also greatly influenced by the treatment. Inasmuch as quantitative determinations were not done routinely, accurate figures cannot be given. The response, however, seemed to parallel the changes in the cell count, although it was not achieved as promptly.

CHANGES IN THE COLLOIDAL GOLD REACTION

The colloidal gold reaction showed a remarkable change toward normal, more so with this treatment than with any other method which

we [15] had used in the past. It was not uncommon to observe grade 3 colloidal gold reactions flatten out to a row of zeros. The colloidal gold curve reversed to normal in 50 per cent of the cases during the first year of observation and in 70 per cent during the second year of observation. The colloidal gold curve was normal in 15.2 per cent of the cases before treatment was given.

Tables 6 and 7 show the changes in the colloidal gold reactions as a result of therapy. The distinctly abnormal colloidal gold curve, such as 5555432100, is designated as grade 3; a less intense reaction, as grade 2, and one with minimal changes, as grade 1.

CHANGES IN THE WASSERMANN REACTION OF THE SPINAL FLUID

The titer of the spinal fluid in the Wassermann test responded less satisfactory to the treatment than did other elements of the spinal fluid. The tendency of the Wassermann reactions to reverse to normal

TABLE 8.—*Changes in the Wassermann Reaction of the Spinal Fluid*

Period of Observation	No Change	Decreased	Decreased to Normal	Increased	Total
120 to 365 days.....	23 (45%)	23 (45%)	4 (8.0%)	1 (2%)	51
365 days +.....	6 (29%)	8 (38%)	7 (32.4%)	0	21

TABLE 9.—*Changes in Serologic Titer of the Blood*

Period of Observation	No Change	Decreased	Returned to Normal	Increased	Total
120 to 365 days.....	15 (31.4%)	24 (50%)	7 (14.5%)	2 (4.1%)	48
365 days +.....	6 (28.2%)	10 (47%)	3 (14.1%)	2 (9.4%)	21

increased as the period of observation was lengthened; i. e., they became normal in 8 per cent of the cases in the first year and in 32.4 per cent in the second year. Table 8 shows these observations.

CHANGES OBSERVED IN SEROLOGIC TESTS OF THE BLOOD

Although a decrease in serologic titer was noted in 64.5 per cent of the cases during the first year of observation, in only 14.5 per cent did the titer return to normal. Longer observation did not affect these percentages.

REACTION TO TREATMENT

The most serious reaction noted was a severe Herxheimer reaction in a white man aged 43, who had dementia paralytica. He had been receiving penicillin sodium, 20,000 units every three hours around the clock for thirty-six hours, when the reaction occurred. He had

15. Epstein, N. N.: Artificial Fever as an Adjunct in the Treatment of Neurosyphilis, Arch. Dermat. & Syph. **37**:254-266 (Feb.) 1938.

had his first fever treatment twelve hours before. He then became disoriented, confused, incontinent, agitated and convulsive. He was transferred to the detention ward of the San Francisco Psychopathic Hospital, where he recovered uneventfully.

A second patient, not included in this series, had a similar reaction. He was a white man, aged 38, who had been receiving 50,000 units of aqueous penicillin sodium intramuscularly every three hours around the clock for five days, subsequent to an emergency appendectomy. Reexamination showed the presence of dementia paralytica clinically and serologically. On the fifth postoperative day, the patient became violently agitated, disoriented and confused and had visual hallucinations. Penicillin therapy was discontinued, and the reaction subsided within forty-eight hours. Penicillin therapy was reinstituted without further untoward effects.

Further evidence of therapeutic shock was noted in the group of 28 patients who received aqueous penicillin sodium at regular intervals around the clock. In 14 of these the temperature rose, varying between 37.4 and 39.4 C. (99.3 and 102.9 F.) within twenty-four hours of the institution of penicillin therapy. In the majority of the patients who exhibited this early febrile response, the temperature did not rise above 38 C. (100.4 F.) and it receded to normal within twelve hours.

Urticaria was noted in 3 of the 87 patients treated; 2 of the patients had received aqueous penicillin sodium, and 1 patient had been given penicillin in oil and wax. A dermatophytosis-like reaction of the hands and feet occurred in 1 patient, and an erythematous eruption of the groins, lower portion of the abdomen and thighs was observed in another. The latter case was the only one in which penicillin therapy had to be discontinued.

Local reactions to penicillin in oil and wax were common during the first year of its use. However, after the introduction of the emulsions which are fluid at room temperature, no severe local reactions at the site of the injections were noted.

The fever therapy was well tolerated in most instances and in only 1 case in this series was it necessary to discontinue the fever therapy because of respiratory difficulty. Nausea and vomiting, immediately after treatment, occurred in several patients. In 1 case the fever therapy was discontinued after nine treatments because of these symptoms. Herpes simplex was common after the first treatment.

COMMENT

There is no doubt that penicillin is the most effective therapeutic agent for neurosyphilis which has been introduced up to the present time. Stokes [2d] found that the best therapeutic response that one can expect to obtain from penicillin alone, regardless of dosage or repeti-

tion of courses of therapy, is improvement in 70 per cent of the patients treated. This, of course, is far better than any that could be accomplished with any other single therapeutic procedure. It is evident, in spite of the remarkable effects thus far observed with the penicillin therapy of neurosyphilis, that this therapy has its limitations. This fact is further substantiated by observation of patients who are not benefited either clinically or serologically by the administration of penicillin and those who suffer relapses after temporary benefit.

These findings have an important bearing on the problem of whether or not the combination of artificial fever therapy and the administration of penicillin offers more to the patient with neurosyphilis than does penicillin alone.

If one may judge from the experimental and clinical data already referred to, it would seem logical that the administration of penicillin combined with artificial fever therapy should give therapeutic results superior to those obtained with either alone. In the small series of patients reported here, the over-all percentage of improvement obtained during the first year of observation was about 70 per cent. During the second year of observation this percentage rose to 87 per cent. These findings are of more significance when the fact that approximately one half of our patients had dementia paralytica is taken into consideration.

The case of S. S., a white woman aged 43 with early dementia paralytica, illustrates the effectiveness of artiffcial fever therapy after treatment with penicillin apparently had failed to improve her spinal fluid abnormalities and subjective symptoms. In April 1946 she received 4,500,000 units of penicillin sodium. On Sept. 5, 1946, her spinal fluid showed 91 cells (lymphocytes), 88 mg. of protein per hundred cubic centimeters, a colloidal gold curve of 555444332 and a strongly positive Wassermann reaction. Between Nov. 29, 1946 and Jan. 29, 1947, the patient received ten weekly pyrexial treatments. On May 5, 1947, the spinal fluid showed 4 lymphocytes, a trace of globulin, a colloidal gold curve of 0000000000 and a Wassermann reaction of 4 units. This improvement was maintained when the spinal fluid was reexamined four months later.

The Herxheimer reactions in the central nervous system which have been noted during penicillin therapy are important, not only from the standpoint of injury to the patient, but also because they possibly indicate a special capacity of penicillin to destroy T. pallidum in the central nervous system.

Callaway [5] was the first to point out the common occurrence of this reaction in the central nervous system. He found that 16 per cent of patients with neurosyphilis had Herxheimer reactions during penicillin therapy. Curtis and others [16] observed that this reaction is not

16. Curtis.[7] Stokes, Steiger and Gammon.[2d] Tucker, H. A., and Robinson, R. C. V.: Neurosyphilitic Patients Treated with Penicillin: Probable Herxheimer Reactions, J. A. M. A. **132**:281-283 (Oct. 5) 1946.

17. Footnote deleted on proof.

infrequent in neurosyphilitic patients receiving penicillin. In our series of 87 patients with neurosyphilis there was only 1 patient in whom definite neurologic symptoms of a Herxheimer reaction developed. Several others showed evidence of therapeutic shock by a rise in temperature shortly after penicillin therapy had been instituted. It is certain that penicillin causes this reaction in the central nervous system much more commonly than does any other antisyphilitic remedy. This is probably due to the ability of penicillin to act readily on T. pallidum in the central nervous system. In turn, this ability probably accounts for penicillin's remarkable effect on the serologic and clinical course of neurosyphilis.

In this series of patients an attempt was made to give each person fifty hours of artificial fever as well as the penicillin therapy. This amount is empiric, and it is probable that the benefit of fever can be obtained by fewer treatments. It may be necessary to administer the artificial fever only during the time the patient is receiving penicillin.

SUMMARY AND CONCLUSIONS

Eighty-seven patients with various forms of neurosyphilis were treated with penicillin combined with artificial fever therapy.

Penicillin was administered in two forms: (*a*) aqueous penicillin sodium, intramuscularly, every three hours around the clock over a fourteen-day period, for a total dose of 4,500,000 units, and (*b*) penicillin calcium suspended in peanut oil containing 4.5 per cent white wax U. S. P., administered in daily single intramuscular injections of 300,000 units each for twenty days, for a total of 6,000,000 units.

Artificial fever therapy was administered by the blanket method during and subsequent to the penicillin course. Five hours of a temperature over 40 C. (104 F.) was considered a single treatment. Most of the patients received a total of fifty hours of fever therapy.

The data on 55 of the patients treated are presented. Twenty-five of these patients had clinical and serologic evidence of paresis. Fifty-five were observed for from 120 to 365 days, 23 were observed for longer periods, and a few were in their third year of post-treatment observation at the time of writing.

The clinical response in the patients with dementia paralytica and meningovascular neurosyphilis was satisfactory. Little change in the clinical condition was noted in those with tabes dorsalis.

The response in regard to spinal fluid abnormalities was excellent. Definite improvement in the spinal fluid signs was noted in 70 per cent of the patients during the first year of post-treatment observation and in 87 per cent of those observed for a longer period.

The cell count, protein content and colloidal gold reaction of the spinal fluid had a tendency to reverse to normal promptly. The Wassermann reaction did not respond as satisfactorily.

The reactions to serologic tests of the blood became negative in only 14.5 per cent of the patients during the first year of observation. This percentage did not change during the second year of observation.

Two severe Herxheimer reactions in the central nervous system were observed. A rise in temperature during the first twenty-four hours of aqueous penicillin sodium therapy was noted in 14 of 28 patients so treated.

The fever therapy was well tolerated by all but 2 patients.

The combination of penicillin and fever therapy gave better effects in our hands than did chemotherapy combined with fever therapy.

Penicillin therapy of neurosyphilis, although superior to any other single therapeutic procedure, has its limitations.

The effects of artificial fever combined with penicillin therapy should continue to be investigated because of (1) the known effects of artificial fever on the clinical course and spinal fluid abnormalities of neurosyphilis and (2) the experimental data which indicate that elevation of temperature in vitro and in vivo enhances the spirocheticidal properities of penicillin.

ABSTRACT OF DISCUSSION

DR. CHARLES R. REIN, New York: Dr. Epstein and Dr. Key are to be congratulated for their fine report on the treatment of neurosyphilis with penicillin combined with artificial fever induced by the blanket method. They are of the opinion that the combination of penicillin and fever therapy gave better effects than did chemotherapy combined with fever treatment. Moore, Rose and O'Leary also recommended the combination of penicillin and fever therapy, whereas Curtis showed that penicillin was as effective in the treatment of neurosyphilis when used alone as when combined with fever therapy.

Stokes found that the best therapeutic response that one could expect to obtain from the administration of penicillin alone, regardless of dosage and repetition of courses of therapy, is improvement of 70 per cent of patients treated. Although this is better than that which could be achieved by any other single therapeutic procedure, Epstein and Key have expressed the opinion that the addition of fever therapy might give results superior to those achieved with either penicillin or fever alone. The belief was stated by Dattner and Thomas that the fever therapy is not necessary. Since April 1944 they have treated approximately 400 patients at Bellevue Hospital with various forms of neurosyphilis exclusively with intramuscular injections of penicillin. Of these persons, 301 received 2,000,000 to 6,000,000 units of penicillin and have been followed for from six to forty-five months. The evaluation of therapy in their group was based almost entirely on the results of repeated examination of the spinal fluid. There were thirty-four failures of treatment (11.3 per cent) following a single course of varying doses of penicillin. However, of the 34 patients for whom treatment was listed as having failed, 19 responded favorably to a second course of treatment with larger doses of penicillin. The remaining 15 patients have not yet had adequate periods

of follow-up for evaluation at this time, although they are all showing a satisfactory trend. Only 1 patient has had a second relapse, with the need for additional retreatment. The excellent results reported by Dattner and Thomas would indicate that fever therapy may not be required. Even if the addition of fever should cause a prompter or earlier improvement of the spinal fluid findings, the end results over long periods of time seem to indicate that treatment with penicillin alone is as effective as and of course much safer than penicillin and fever therapy. Although Epstein and Key had to discontinue fever therapy in only 2 patients because of respiratory difficulties and repeated attacks of nausea and vomiting, serious and even fatal untoward reactions associated with other forms of induced fever therapy may occur in from 5 to 20 per cent of patients. Furthermore, the cost of hospitalization and nursing care, as well as time lost from employment, especially by the asymptomatic group, must also be considered.

It is well known that fever alone is effective on the clinical course and spinal fluid abnormalities of neurosyphilis. It has been established, in experimental syphilis, that increase in temperature either in vitro or in vivo enhances the spirocheticidal property of penicillin. Considering the excellent reports made by Dattner and Thomas and by Curtis, it is doubtful whether the addition of fever therapy to the administration of penicillin is necessary or justified for all patients with neurosyphilis.

DR. ARTHUR C. CURTIS, Ann Arbor, Mich.: I enjoyed hearing Dr. Epstein's excellent paper. Many of those who in 1944 heard Dr. Stokes present his first studies [2a] on the use of penicillin in syphilis of the central nervous system were biased in their opinions. It was my feeling at the time that malaria therapy would do more than the administration of penicillin and that a combination of both probably would be the best form of therapy. Through the cooperation of the National Research Council, my associates and I began two methods of treatment of syphilis of the central nervous system, which we have continued to date (Curtis, A. C.; Burns, R. E., and Norton, D. H.: Neurosyphilis: Treatment with Penicillin Alone and with a Combination of Penicillin and Malaria, *Am. J. Syph., Gonor. & Ven. Dis.* **31**:618-632 [Nov.] 1947).

One regimen consisted in the administration of penicillin alone in total doses of 4,000,000 units, over a period of twelve and one-half days. In the other method the penicillin dose was the same but, in addition, eight to twelve febrile episodes induced by malaria were given.

In 750 patients treated since 1945, the over-all results in all types of syphilis of the central nervous system show that treatment with malaria and penicillin combined does little more than the administration of penicillin alone, except to increase the mortality rate. In the group which had both therapeutic malaria and treatment with penicillin, improvement in the spinal fluid findings was more rapid, but the net result after two years' observation was no better. In a group of more than 100 patients with dementia paralytica and its tabetic form, combined penicillin-malaria therapy seemed to be slightly better than treatment with penicillin alone after two years' observation. It is too early to predict what the eventual outcome will be in this group.

DR. JOSEPH V. KLAUDER, Philadelphia: It may not be too much digression to take this opportunity to make a plea for the early diagnosis of optic atrophy. Among 397 patients with syphilitic primary optic atrophy at Wills Hospital 61 per cent when first seen were industrially blind (had visual acuity with correction of less than 6/60). Diagnosis of optic atrophy is usually made at the time of impaired visual acuity. To facilitate early diagnosis routine ophthalmologic

examination should be conducted on all patients with neurosyphilis (Klauder, J. V.; Meyer, G. P., and Gross, B. A.: Syphilitic Primary Optic Atrophy as a Cause of Blindness: Importance of Early Diagnosis, *Am. J. Syph., Gonor. & Ven. Dis.* **32**:574-586 [Nov.] 1948).

DR. JOHN RAUSCHKOLB, Cleveland: One must take into consideration that syphilis of the central nervous system is a variable process. Generally, it starts with inflammatory changes and terminates with degenerative changes. Parenchymatous degeneration is almost always preceded by inflammatory processes. Physicians are well aware of the fact that arsenical compounds and preparations of the heavy metals are excellent drugs to use in overcoming these early inflammatory changes. As the process becomes more chronic and degenerative, pyrotherapy, be it either externally and artifically produced fever or internally produced foreign protein or malarial therapy, has been the method of choice. Penicillin probably acts therapeutically more on the inflammatory changes of the central nervous system than on the degenerative changes. It has all the excellent qualities of chemotherapy, with minimal toxicity.

At Cleveland City Hospital, when possible, a combination of treatment with penicillin and fever therapy in the form of therapeutic malaria is still used to combat the various stages of syphilis of the central nervous system. With this combination of therapy it is hoped that the inflammatory changes will be eradicated by administration of penicillin and that the progress of the degenerative changes will be prevented by malaria therapy.

DR. NORMAN EPSTEIN, San Francisco: Time does not permit me to present more details of the paper nor to give credit to the many men here who have contributed to this subject. Dr. Rein summarized the problem very well. Do we need fever therapy, or can we do without it? Shall we discard fever therapy, and will penicillin solve the problem alone? If we agree that there are some patients whom penicillin therapy does not cure or even help, then we should not discard other methods of known value. That is my feeling in this matter. In the present state of knowledge I believe that fever therapy should not be withheld from a patient with signs and symptoms of dementia paralytica. Fever therapy should be combined with the administration of penicillin, also, in cases in which treatment with penicillin alone has failed to give a satisfactory therapeutic result.

In patients in whom degenerative processes are occurring in the central nervous system time is an important element. The sooner the processes are arrested, the better the outlook will be for the patient. Fever therapy tends to arrest these degenerative changes much faster than does treatment with penicillin.

I wish to thank the discussants for their excellent comments.

PARALYSIS OF CRANIAL NERVES COMPLICATING HERPES ZOSTER

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HERPES zoster is presumed to be caused by a filtrable virus similar to, if not identical with, that causing varicella. This virus is capable of producing an acute inflammatory process in cranial or spinal nerves, ganglions, dorsal and ventral spinal nerve roots, posterior gray matter of the spinal cord or the adjacent meninges, and the disease may therefore be appropriately termed a neuroganglioradiculomeningomyelitis. Clinical manifestations consist of a cutaneous grouped vesicular eruption on an erythematous base, neuralgia and, occasionally, paralysis.

Many predisposing factors have been suggested as favoring the establishment of herpes zoster: seasonal variations; trauma; arsenical drugs; dental pathologic changes; spondylitis, dyscrasias of the blood, including leukemia, Hodgkin's disease and lymphosarcoma; malignant visceral tumors, and tabes dorsalis. Sex is not a factor, and herpes zoster has been reported in all age groups, although it occurs most frequently in middle-aged or elderly persons. Statistical proof that herpes zoster is commoner in connection with Hodgkin's disease, lymphosarcoma and leukemia is wanting, although clinically it is believed that it is. Herpes zoster when a concomitant manifestation of the various types of leukemia occurs most frequently in middle-aged men with lymphatic leukemia, and in such cases the lesions are often of the generalized type.[1]

Usually herpes zoster is a benign infection affecting principally the sensory portion of the nervous system. Although the severity and duration vary, the course is self limited, terminating usually without sequelae in a few weeks. In exceptional cases severe pain persists for

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1. Wile, U. J., and Holman, H. H.: Generalized Herpes Zoster Associated with Leukemia, Arch. Dermat. & Syph. **42**:587-592 (Oct.) 1940.

years. This is especially true of elderly persons. Motor symptoms occur infrequently, although both upper and lower motor neuron paralysis complicating herpes zoster has been recorded. Of the paralysis of the lower motor neurons facial paralysis associated with otalgia following otic herpes zoster is the commonest. J. Ramsay Hunt, whose name is synonymous with this syndrome, originally described several such cases in 1907.[2] The next most frequently reported palsy is oculomotor muscular paralysis complicating herpes zoster involving the ophthalmic division of the fifth cranial nerve. Motor disturbances of the trunk and of the upper and lower extremities less common.[3]

Hunt described the following variations of geniculate herpes zoster involving the seventh cranial nerve: (1) herpes zoster oticus, (2) herpes zoster oticus with facial paralysis, (3) herpes zoster oticus with facial paralysis and hypacusis and (4) herpes zoster oticus with facial paralysis and Ménière's syndrome. Because of their intimate connections Hunt stated the opinion that the ganglions of the fifth, seventh, eighth, ninth and tenth cranial nerves and of the second, third and fourth cervical nerves represent a continuous ganglionic series, all parts having the same embryonal origin in the neural ridge. He therefore recognized the possible involvement of cranial ganglions other than the geniculate, but he expressed the belief that such involvement was always secondary to geniculate ganglionitis and never an independently existing infection. Hunt stressed the necessity of a ganglionitis and expressed disagreement with the contention that zoster could spread by extension along nerve roots. Pathologic investigations have proved this assumption invalid.[4] A ganglionitis need not always be present. It has also been demonstrated that secondary degeneration may be located in the meninges, the posterior columns of the spinal cord, the spinal nerve roots and the fibers of peripheral nerves.

To comprehend clearly the varied manifestations of herpes zoster, especially in regard to the head and neck, it is necessary for one to realize that the presence of herpes zoster in any dermatome denotes not only an infection of the particular neural structures supplying that zone but also the possibility of an ascending or descending neuritis involving the structures of one or more nerves whose pathways connect with the originally infected nerve. These connections may be utilized in explain-

2. Hunt, J. R.: On Herpetic Inflammations of the Geniculate Ganglion, J. Nerv. & Ment. Dis. **34**:73, 1907.

3. Taterka, J. H., and O'Sullivan, M. E.: The Motor Complications of Herpes Zoster, J. A. M. A. **122**:737-739 (July 10) 1943.

4. Denny-Brown, D.; Adams, R., and Fitzgerald, P.: Pathologic Features of Herpes Zoster: Note on "Geniculate Herpes," Arch. Neurol. & Psychiat. **51**:216-231 (March) 1944.

ing motor palsies associated with herpes zoster, irrespective of whether the localization of the eruption is remote or in the vicinity of the paralysis. Many cases of the so-called Hunt syndrome in reality probably involve two or more nerves, rather than the seventh cranial nerve alone. Herpes zoster occipitocollaris limited to the dermatomes of the second and third cervical nerves depends on connecting tracts existing between these nerves and the seventh cranial nerve in producing a facial paralysis. Oculomotor nerves of the eye (third, fourth and sixth cranial nerves) may be involved in the course of zoster of remote localization.[5] So, also, in the case reports to follow, are intimate neural circuits seen to be of prime importance in an endeavor to associate and

Fig. 1 (case 1).—A photograph taken shortly after the patient's first admission, showing zosteric involvement of the left maxillary dermatome associated with purulent exudate from the left eye. Ability to approximate the left eyelids and the presence of wrinkles testified to the absence of a peripheral facial paralysis at that time.

explain zosteric involvement of the sensory distribution of one nerve and the subsequent motor paralysis of another cranial nerve.

REPORT OF CASES

CASE 1.—*Herpes zoster maxillaris (second division of the trigeminal nerve) with facial paralysis.*

O. J., a 70 year old Negro, was admitted to the dermatologic wards of Bellevue Hospital on Nov. 22, 1947, at which time he complained of swelling of the left cheek and eyelids, of five days' duration, and of slight dizziness. Pain had not been present at any time during the course of his illness. His past history was irrelevant except for pneumonia in 1917 and hospitalization

5. Edgerton, A. E.: Herpes Zoster Ophthalmicus: Report of Cases and Review of Literature, Arch. Ophth. **34**:40-62 (July); 114-153 (Aug.) 1945.

of ten days' duration in November 1940 for acute left epididymitis caused by Escherichia coli, which disease had responded to therapy.

Examination.—On the patient's admission a vesicular eruption on an erythematous base involved the left side of the nose, the upper lip and the left cheek (fig. 1). A few vesicles were present on the left side of the forehead. The left periorbital region was swollen and the palpebral fissure nearly closed as the result of the edema. The left conjunctiva was inflamed, and a purulent discharge was present. Small whitish vesicles, arranged singly and in groups, were observed on the inner aspect of the upper lip, the gingiva, the hard and soft palate, the uvula and the buccal mucosa, sharply limited to the left side of these structures, including the uvula (fig. 2). The inner aspect of the left nostril was covered with crusts. The other abnormal findings were bilateral submaxillary adenopathy, more evident on the left side, and a reducible right inguinal hernia; vitiligo of the legs and inner aspect of the prepuce was noted. The rectal temperature on admission was 104.2 F., and the blood pressure was 134 systolic and 64 diastolic.

On the third day after the patient's admission to the hospital the left eyelids were adherent with a purulent exudate. The cornea was clear. Therapy consisted

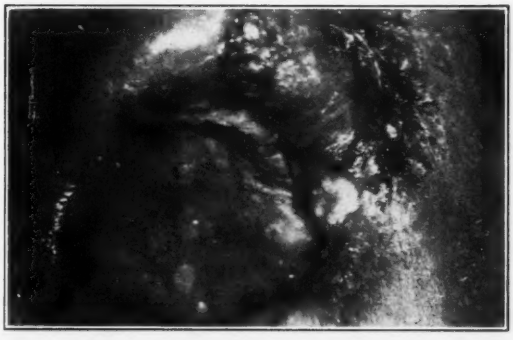

Fig. 2 (case 1).—Another photograph of O. J., also taken shortly after his first admission, illustrating zosteric involvement of the upper lip and the hard and soft palates, limited to the left side of these structures. Simultaneous involvement of the hard and soft palates is a rare occurrence, having been recorded on only 4 occasions.[10]

of administration of penicillin, 40,000 units every three hours, to combat secondary infection; thiamine hydrochloride, 30 mg. three times daily, and nicotinic acid, 50 mg. three times daily. Compresses soaked in saline solution and ointment containing mercury bichloride were applied for the relief of the ocular symptoms. The complement fixation test for syphilis had negative reactions. A complete blood count showed these values: erythrocytes, 5,380,000; hemoglobin, 14.5 Gm., and leukocytes, 25,250, with 34 per cent polymorphonuclear cells, 62 per cent lymphocytes and 4 per cent mononuclear cells.

The course in the hospital was uneventful, and on the thirteenth day after admission the patient was discharged to the outpatient department clinic for treatment of the ectropion which had resulted from cicatrization of the left infraorbital tissues.

The patient was readmitted on December 11, seven days after his discharge from the hospital, complaining of inability to move the left side of his face, of

five or six days' duration, and also of swelling and pain over the lateral aspect of the left side of his neck since the morning of his second admission. He also complained of slight dizziness.

Physical examination revealed secondary infection on the left side of the nose and the upper lip, with healing in the areas initially involved. No herpetic lesions were noted on the tympanic membrane, the external auditory meatus or in the region of the left ear. An inflamed, tender, nonfluctuant mass about 7 or 8 cm. in width was present on the left lateral aspect of the neck not involving the mastoid region. A complete, hence peripheral, paralysis was present over the left side of the forehead and face (fig. 3). Because of the ectropion and partially because of the paralysis, the patient was unable to close his left eye. The opening power of both upper lids was unimpaired, as would be expected, since this ability is controlled by the third cranial nerve. The corneal reflex was absent on the left side, but the consensual corneal reflex was present, showing damage to the seventh

Fig. 3 (case 1).—A photograph of the patient at the time of his second admission (thirty-five days after the onset of the cutaneous eruption) in which flaccid paralysis of the left side of his face may be seen. Note the obvious inability of the patient to wrinkle his forehead or to show his teeth on the involved side. The ectropion is clearly visible.

cranial nerve but not to any sensory portion (ciliary nerves) of the fifth cranial nerve. There was no sensory impairment in the region of the ophthalmic or the mandibular division of the trigeminal nerve, but the senses of pain, touch and temperature were absent in the area innervated by the maxillary division on the left side. The muscles of mastication were unaffected. Sensation of taste on the anterolateral aspect of the left side of the tongue was apparently unimpaired, this finding indicating that the chorda tympani nerve was not involved. The Romberg and other neurologic signs were absent. The blood pressure was 118 systolic and 54 diastolic. Electrical testing showed no reaction of degeneration.

On the fourth hospital day the cervical mass, then fluctuant, was incised, and a small lobulation of pus and necrotic tissue was removed. On culture hemolytic streptococci were obtained. Consultation confirmed our opinion that the abscess

had no relation to the preceding facial paralysis. Progressive improvement of the paralysis, with gradual return of muscle power, was noted. Following his hospital discharge the patient failed to attend the hematology clinic for further investigation to rule out the presence of any possible blood dyscrasia. No residuum of the paralysis was present when the patient was observed six months after the onset of his herpetic eruption (fig. 4).

Fig. 4 (case 1).—O. J., six months after the onset of the herpes zoster eruption. Cicatricial deformity is present in the involved region. No residuum of the facial paralysis is present.

Laboratory examination of the blood produced the following observations:

Dec. 12, 1947	Dec. 22, 1947	Jan. 5, 1948
Erythrocytes.....4,510,000	Erythrocytes.....4,590,000	Erythrocytes.....4,010,000
Hemoglobin.....10.5 Gm.	Hemoglobin.....13.5 Gm.	Hemoglobin.....11.5 Gm.
Leukocytes.....22,850	Leukocytes.....23,750	Differential Count:
Polymorphonuclear cells..28%	Polymorphonuclear cells..32%	Polymorphonuclear cells..29%
Lymphocytes.....72%	Lymphocytes.....64%	Lymphocytes.....70%
	Mononuclear cells.....1%	Basophils.....1%
	Basophils.....2%	No sickling was noted on the blood smear.

Pathologic Report on Surgical Specimen (Dec. 14, 1948).—The section consisted of a lymph node. There were present large spaces filled with red blood cells, polymorphonuclear leukocytes, a small number of eosinophils and mononuclear cells and, in some areas, a large number of foam cells. These spaces appeared to be enormously dilated vascular channels, and in some of them there were large amounts of coagulated fibrin suggestive of thrombosis. The red cells which were not hemolyzed were sickled. At the margin of the section there was an inflammatory reaction characterized by young granulation tissue, polymorphonuclear leukocytes, mononuclear cells and foam cells. Elsewhere within the structure there was mild hyperplasia of the reticulum cells of the sinuses. Bismarck brown stain failed to reveal the presence of an appreciable number of organisms. The Van Gieson stain for elastin failed to reveal any elastic fibers in the walls of the dilated channels previously described or in the walls of the other veins. The pathologic diagnosis was sicklemia and acute lymphadenitis, with formation of an abscess.

CASE 2.—*Herpes zoster maxillaris with facial paralysis.*

H. R., an 80 year old white man, was admitted to Bellevue Hospital on Dec. 7, 1947, with a painless eruption over the right cheek, of one week's duration. The past history was noncontributory.

An extensive vesicular eruption on an inflammatory base was present over the right maxillary dermatome of the trigeminal nerve. A few aberrant vesicles were also present on the lateral aspect of the right side of the patient's forehead. Eroded vesicles were also observed on the hard and soft palate and on the buccal mucosa, limited to the right side. The right palpebral fissure was closed as a result of periorbital edema. The right conjunctiva was injected, but the cornea was not involved. Sensations of touch, temperature and pain were absent over the area of herpetic involvement on the right cheek. No herpetic lesions or other pathologic changes were found in the auricular or periauricular areas or on the neck or the tympanic membrane. The rectal temperature on the patient's admission was 101.4 F.

Bearing in mind the facial palsy in case 1 and noting the similarity of the signs and symptoms in these 2 cases, we deemed it advisable to follow this patient in the hospital for possible motor complications. Unfortunately for the patient, the vigil was rewarded, as on the twenty-first day of hospitalization a peripheral facial paralysis developed. Neurologic signs characterizing this phenomenon were present, and, as in the first case, the sensory fibers of taste were apparently not affected. Therapy consisted of penicillin, 40,000 units every three hours for a total of seventy doses to control secondary infection; thiamine hydrochloride intramuscularly, and instillations of zinc sulfate into the eye. This patient also showed progressive improvement of the paralysis, with gradual and complete return of muscle power within a six month period.

The laboratory data on the blood on December 8 were as follows: erythrocytes, 5,940,000; hemoglobin, 16.5 Gm.; leukocytes, 6,050, with 60 per cent polymorphonuclear cells, 35 per cent lymphocytes and 5 per cent mononuclear cells. Serologic reactions for syphilis were negative.

NEUROLOGIC ASPECTS

Despite the importance of knowledge concerning the various neural pathways connecting the cranial and cervical nerves in an understanding of the numerous combinations of herpes zoster and paralysis which are likely to occur in the head, such a neurologic discussion would be beyond

the realm of this article. A brief discussion of the tracts involved in the cases under consideration here, namely the fifth (trigeminal) and the seventh (facial) cranial nerves and the sphenopalatine ganglion is nevertheless indicated. The trigeminal and facial nerves are related by means of the superficial petrosal nerves, large and small.

The facial nerve is both sensory and motor. It contains the following fibers: (1) efferent fibers to superficial muscles of the face and scalp and the platysma, the stylohyoid, the posterior belly of the digastric and the stapedius; (2) autonomic efferent fibers to the submaxillary and sphenopalatine ganglions, supplying the submaxillary, sublingual and lacrimal glands and the mucous membrane of the nose and the roof of the mouth; (3) afferent fibers of taste from the anterior two thirds of the tongue, and (4) probably a few afferent fibers which,

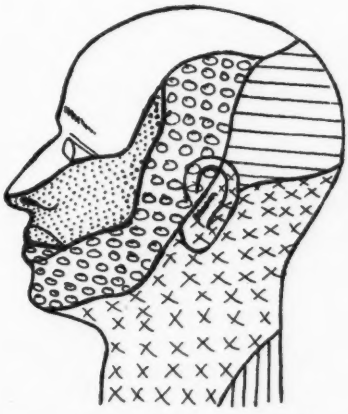

Fig. 5.—General sensory faciocraniocervical dermatomes. The blank area is that supplied by the ophthalmic (V_1) division of the trigeminal nerve; the stippled portion, by the maxillary (V_2) division; the circled area, by the mandibular (V_3) division; the cross hatched part, by the second cervical nerve; the area of crosses, by the third cervical nerve, and the vertically hatched area, by the fourth cervical nerve.

together with similar fibers from the ninth and tenth nerves, aid in innervation of the external auditory meatus and the skin back of the ear. Although the functional significance of many of the direct branches of communication of the facial nerve, including those with the fifth, eighth, ninth and tenth cranial and cervical nerves, is unknown, each, however, theoretically offers a potential avenue of extension by which an ascending or descending neuritis resulting from herpes zoster could affect other cranial nerves. The ramifications of the seventh nerve and also its nucleus receive terminals from many sources, including cranial nerves other than those mentioned above.

The trigeminal nerve has three main divisions: ophthalmic, maxillary and mandibular (fig. 5). The first two are wholly sensory, but the mandibular branch also incorporates motor fibers to the muscles of mastication. The ophthalmic branch innervates the forehead, the upper eyelid, the cornea, the conjunctiva, the anterolateral aspect of the nose, the mucous membrane of the nasal vestibule and the frontal sinus. The maxillary division supplies the upper lip, the lateral and posterior portions of the nose, the cheek, the anterior portion of the temple and the mucous membrane of the nose, the upper jaw, the upper teeth and the roof of the mouth to the palatopharyngeal arch. The sensory branch of the mandibular division innervates the lower lip, the chin, the posterior portion of the cheek and temple, the external ear

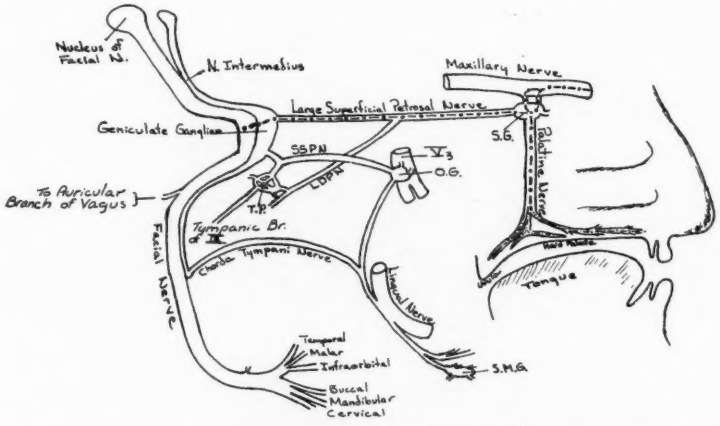

Fig. 6.—The facial nerve and its communicating branches. *O.G.* signifies the otic ganglion; *S.G.*, the sphenopalatine ganglion; *S.M.G.*, the submaxillary ganglion; V_3, the mandibular nerve; *SSPN*, the small superficial petrosal nerve; *LDPN*, the large deep petrosal nerve, and *T.P.*, the tympanic plexus. The line of dots and dashes represents the assumed course of infection.

and the mucous membrane of the lower jaw, the lower teeth, the cheeks, the anterior two thirds of the tongue and the floor of the mouth. All three divisions, together with fibers from the seventh, ninth and tenth cranial nerves, contribute to the sensory innervation of the dura, and these connections are to be remembered when signs of meningitis are present with herpes zoster of the head or neck.

The sphenopalatine ganglion is the largest autonomic ganglion associated with the trigeminal nerve and receives a sensory, a motor (parasympathetic) and a sympathetic root derived from the maxillary nerve, the seventh cranial nerve and the carotid plexus, respectively. The palatine nerves are distributed to the hard and soft palate, the

tonsils, the uvula and the lining membrane of the nasal cavity. Most of their fibers are derived from the sphenopalatine branches of the maxillary nerve.[6]

In both cases reported there was facial nerve involvement, most likely from initial infection of the maxillary nerve with extension via the sphenopalatine ganglion and the large superior petrosal nerve, as shown in figure 6.

THERAPY

The management of herpes zoster is symptomatic. Since pain is usually the outstanding complaint, relief is often the main problem of therapy. The patient may require only salicylates or codeine, but in extreme cases even morphine may prove unsuccessful. Although no medication has been discovered which shortens the course of the disease, many drugs may be used to help comfort the patient. Administration of surgical pituitrin® (posterior pituitary solution containing 20 pressor units per cubic centimeter), use of convalescent serum, roentgen therapy, ultraviolet irradiation, diathermy, injection of foreign protein, autohemotherapy and administration of diphtheria antitoxin, thiamine hydrochloride and sodium iodide, among other measures, have all been reported as being helpful in some hands. The cutaneous lesions respond best to an occlusive type of dressing, and therefore collodion, paraffin or pliable paraffin (paressine®), for example, are especially useful for topical application. Residual scar deformities, such as the ectropion cited in case 1, may be sufficiently extensive to warrant plastic surgery. Optic involvement should be treated promptly by an ophthalmologist. It is a clinical prognostic sign that ophthalmic complications are more likely to occur if there is involvement of the nasociliary branch of the ophthalmic division of the fifth cranial nerve, clinically manifested by a vesicular eruption over the anterolateral aspect of the nose. Following facial paralysis residual motor signs may persist, but nearly complete or total recovery is apparently commonest. Faradic current or other types of electrical stimulation may be employed in the treatment of muscular paralysis. Nerve block or surgical sectioning of the nerve or its ganglion may be necessary in severe neuralgias, although even the latter procedure is occasionally unsuccessful in the relief of postherpetic pain in the distribution of the cranial nerves.[8] In such cases neuralgia may be eliminated by stellate and upper thoracic ganglionec-

6. Strong, O. S., and Elwyn, A.: Human Neuroanatomy, Baltimore, Williams & Wilkins Company, 1943. Gray, H.: Anatomy of the Human Body, edited by W. H. Lewis, ed. 24, Philadelphia, Lea & Febiger, 1942.

7. Footnote deleted.

8. Peet, M. M.: Post-Herpetic Trigeminal Neuralgia, J. A. M. A. **92**:1503-1505 (May 4) 1929.

tomy on the same side.[9] This phenomenon suggests the possibility that pain and hyperesthesia may be mediated by afferent sympathetic nerves (many deny the existence of afferent autonomic cells) or that somatic afferent fibers may also travel by way of the autonomic nervous system. Nerve block, since the pathologic change is often proximal to the site of the block, may succeed in relieving only the hyperesthesia, if present, while pain may persist. It is interesting to note that, despite the patients' ages and the rather extensive and destructive involvement, pain was conspicuously absent in both case 1 and case 2. This absence, although difficult to explain, may be due to the involvement of both the sensory somatic (maxillary nerve) and the autonomic (sphenopalatine ganglion) neural systems supplying the area involved.

CONCLUSIONS

One need only know the established complex neural circuits and the functions of the nerves thereby connected to elaborate numerous theoretically possible syndromes capable of resulting from herpes zoster involving one or more components of these networks. It seems reasonable to speculate that, although comparatively few syndromes of the number mathematically possible have been reported, numerous others have occurred but have gone unrecognized. With these neural networks in mind it is possible for one to predict various syndromes, which as yet have not occurred or (more probably) have passed unrecognized, in which zosteric involvement of a sensory nerve is followed by motor complications in another nerve. Many such cases and syndromes would undoubtedly be discovered through physical and neurologic examinations in all cases of herpes zoster. Of particular importance is a follow-up of at least one month in all cases of herpes zoster involving the head and neck, since the neural network is more complex in this region. Failure of adequate follow-up undoubtedly explains the paucity in the literature of reports of motor complications resulting from zosteric inflammation of two or more nerves. Continued observation is essential because the eruption and paralysis never occur simultaneously and the period of latency may be as long as one month or slightly longer.

Any idiopathic facial or other muscular paralysis subsequent to or shortly preceding a herpes zoster eruption of the head should be considered a possible complication of the herpes zoster, and the probable neurologic route of infection should be studied. There is no correlation between the severity of the cutaneous eruption and the presence or absence of motor complications of the involved or other nerves.

9. Hyndman, O. R.: Post-Herpetic Neuralgia in the Distribution of the Cranial Nerves, Arch. Neurol. & Psychiat. **42**:224-232 (Aug.) 1939.

The development of herpes zoster should also suggest the possibility of lymphosarcoma, Hodgkin's disease or leukemia. The possible persistence of post-herpes-zoster pain, scar formation, ophthalmic involvement or, occasionally, paralytic complications should be considered when a prognosis is offered.

The similarity of the 2 cases reported here consists in the following symptoms and signs: (1) herpes zoster of the maxillary division of the fifth cranial (trigeminal) nerve, involving both cutaneous and mucous membrane dermatomes; (2) absence of pain, and (3) ipsilateral peripheral facial paralysis. There findings present the possibility of a clinical syndrome. Our review of the literature in English revealed no case recorded which exactly paralleled those described above. Two interesting cases were reported, however, in which herpes zoster involved the hard and soft palate and nasal mucosa, in addition to being associated with an ipsilateral vesicular auricular eruption, auricular neuralgia and facial palsy.[10] The auricular element in these reported cases suggests the possibility of an associated Hunt syndrome.

SUMMARY

Two cases of facial paralysis complicating herpes zoster involving the maxillary branch of the fifth (trigeminal) nerve are reported. Cutaneous involvement preceded the paralysis by approximately twenty days in case 1 and by twenty-six days in case 2. The similarity of symptoms and signs in both cases is striking.

140 East Fifty-Fourth Street (22).

10. Wakeley, C. P. G., and Mulvany, J. H.: A Rare Feature of the Ramsay Hunt Syndrome, with Some Observations on Sensory System of Seventh Nerve, Lancet **1**:746-750 (April 1) 1939.

RELAPSING FEBRILE NODULAR PANNICULITIS (WEBER-CHRISTIAN DISEASE)

Review of the Literature and Report of a Case

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NEW ORLEANS

RELAPSING febrile nodular panniculitis, or Weber-Christian disease, is characterized by recurring bouts of fever, associated with the appearance of crops of subcutaneous nodules, varying from the size of a pea to several inches in diameter, usually on the thighs and arms and frequently on the abdomen, back and legs. These manifestations may remain separate or become, by confluence, indurated areas of subcutaneous fat. The nodules, which may be either painless or tender to touch, are frequently erythematous and raised above the surface of the normal skin. The pathologic changes appear to be necrosis of the subcutaneous fat, with infiltration by lipophages and eventually fibrosis. Over a period of months the nodules may slowly regress, leaving shallow or deep-pitted areas covered by normal skin.[1] As a rule, no pathologic changes are observed in the other systems of the body, although death from the disease per se has been reported in 4 cases.[2] In a few cases an enlarged spleen and leukopenia have been outstanding features.

To date 43 cases of this syndrome have been reported in the literature. This figure is slightly in excess of that reported in other recent articles, but it has been arrived at by a careful survey of the literature, several reports having been found that have not been

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1. Larkin, V. de P.; DeSanctis, A. G., and Margulis, A. C.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease): Review of Literature, with Report of a Case, Am. J. Dis. Child. **67**:120-125 (Feb.) 1944.

2. (*a*) Bailey, R. J.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), J. A. M. A. **109**:1419-1424 (Oct. 30) 1937. (*b*) Friedman, N. B.: Fatal Panniculitis (Including Autopsy), Arch. Path. **39**:42-46 (Jan.) 1945. (*c*) Miller, J. L., and Kritzler, R. A.: Nodular Nonsuppurative Panniculitis (Failure of Sulfonamide Therapy), Arch. Dermat. & Syph. **47**:82-96 (Jan.) 1943. (*d*) Ungar, H.: Relapsing Febrile Nodular Inflammation of Adipose Tissue (Weber-Christian Syndrome): Case With Autopsy, J. Path. & Bact. **58**:175-185 (April) 1946.

previously included in reviews. Of these, 2 cases [3] are not particularly well authenticated but are included because of their inclusion in Baumgartner's series.[4]

The first case was described by Pfeifer [5] in 1892; the second, concerning which the authors emphasized the role of the macrophage in the lesion, was reported by Gilchrist and Ketron [6] in 1916. Weber,[7] in reporting the third case in 1925, supplied the name "relapsing nonsuppurative nodular panniculitis," and to this Christian [8] added the adjective "febrile" in reporting the fourth case in 1928. "Nonsuppurative" is not used in this paper because several cases of the syndrome have been reported which fulfil all the criteria with the exception that either frank pus [9] or a greenish yellow mucoid material [10] was to be found in the nodules, albeit the material was in each instance sterile.

The fifth and sixth cases were reported by Alderson and Way [11] and Netherton [12] in 1935. Weber,[9b] in reporting the seventh case, suggested iodides as the probable cause in this case, as the onset followed the ingestion of iodides, and a recurrence occurred with a second administraton of them. Brill [13] reported the eighth case and summarized what he

3. (*a*) Pinetti, V., cited by Baumgartner and Riva.[4] (*b*) Puente, cited by Baumgartner and Riva.[4]

4. Baumgartner, W., and Riva, G.: Nodular Inflammation of Adipose Tissue, Helvet. med. acta. (supp. 14) **12**:1-69, 1945.

5. Pfeifer, V.: Ueberwein Fall von herdwein Atrophie des subcutanein Fettgewebes, Arch. f. klin. Med. **50**:438-449, 1892.

6. Gilchrist, T. C., and Ketron, L.: A Unique Case of Atrophy of the Fatty Layer of the Skin, Preceded by the Ingestion of the Fat by Large Phagocytic Cells—Macrophages, Bull. Johns Hopkins Hosp. **27**:291-294 (Oct.) 1916.

7. Weber, F. P.: A Case of Relapsing Nonsuppurative Nodular Panniculitis, Showing Phagocytosis of Subcutaneous Fat Cells by Macrophages, Brit. J. Dermat. **37**:301-311 (July) 1925.

8. Christian, H. A.: Relapsing Febrile Nodular Nonsuppurative Panniculitis, Arch. Int. Med. **42**:338-351 (Sept.) 1928.

9. (*a*) Ungar.[2d] (*b*) Weber, F. P.: A Further Note on Relapsing Febrile Nodular Nonsuppurative Panniculitis, Brit. J. Dermat. **47**:230-233 (June) 1935.

10. (*a*) Binkley, J. S.: Relapsing Febrile Nodular Nonsuppurative Panniculitis, J. A. M. A. **112**:113-116 (July 8) 1939. (*b*) Ives, G.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease) with Report of Case, J. Missouri M. A. **42**:409-410 (July) 1945. (*c*) Shaffer, B.: Liquefying Nodular Panniculitis, Arch. Dermat. & Syph. **38**:535-544 (Oct.) 1938.

11. Alderson, H. E., and Way, S. C.: Relapsing Febrile Nonsuppurative Panniculitis (Weber), Arch. Dermat. & Syph. **27**:440-449 (March) 1933.

12. Netherton, E. W.: Relapsing Nodular Nonsuppurative Panniculitis, Arch. Dermat. & Syph. **28**:258-359 (Aug.) 1933.

13. Brill, I. C.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), in Medical Papers Dedicated to Henry Asbury Christian in Honor of His Sixtieth Birthday, Baltimore, Waverly Press, Inc., 1936, pp. 624-704.

considered the distinguishing clinical features. Bailey [14] in 1937 collected 5 cases from the Mayo Clinic and added them to the literature. In 1 of these cases the course was particularly severe, and the patient died, apparently from the syndrome, but permission for necropsy was refused. There was either a suspected or a definite history of ingestion of bromides or iodides before onset of the syndrome, or exacerbation of the syndrome occurred after administration of the halide in all these 5 cases. Reed and Anderson [15] added the fourteenth case in 1937, followed by Cummins and Lever [16] with 2 cases in 1938, both of which were unusual in that there were striking changes in the walls of the blood vessels in the biopsy sections examined.

Shaffer [10c] reported the seventeenth case under the heading of "liquefying nodular panniculitis" and considered his case unique in that the nodules contained a yellowish brown fluid which would eventually rupture to the exterior. Binkley [10a] shortly afterward reported a similar case, in a 36 year old woman, in which the cystic masses were first found in the breasts and later spread to the arms and legs. Puente's [3b] case, reported in 1938, is included here as the eighteenth, although it, occurring in a woman aged 48, was the only one in which micro-organisms (Staphylococcus aureus) were found in the nodules. In Mengoli's case [17] the patient was afflicted while convalescing from typhus. Hazel and Lamb [18] in January 1940 reported the case of an 11 year old girl with lesions of the abdomen and legs. The lesions clinically resembled those of morphea, or localized scleroderma. The patient was afebrile while observed, but otherwise the findings were typical of Weber-Christian disease.

Tilden, Gotshalk and Avakian [19] added the twenty-second and twenty-third cases in 1940. In the first of these the patient died of tuberculosis eight and one-half months after having been apparently cured of his panniculitis. Permission for necropsy was obtained, but examination revealed nothing significant other than the tuberculosis.

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14. Bailey, R. J.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Chrstian Disease), J. A. M. A. **109**:1419-1424 (Oct. 30) 1937.

15. Reed, A. C., and Anderson, H. H.: Relapsing Nonsuppurative Panniculitis, California & West. Med. **47**:325 (Nov.) 1937.

16. Cummins, L. J., and Lever, W. F.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), Arch. Dermat. & Syph. **38**:415-426 (Sept.) 1938.

17. Mengoli, cited by Baumgartner and Riva.[4]

18. Hazel, O. G., and Lamb, J.: Primary Panniculitis Afebrile in Type and Associated with Sclerodermatous-like Changes, J. Oklahoma M. A. **33**:1-5 (Jan.) 1940.

19. Tilden, I. L.; Gotshalk, H. C., and Avakian, E. V.: Relapsing Febrile Nonsuppurative Panniculitis, Arch. Dermat. & Syph. **41**:681-689 (April) 1940.

Skiold [20] in 1940 described a clinically typical case, the patient being a 51 year old woman with lesions beginning on the lower extremities and a temperature as high as 104 F. During the course of a year some of the lesions healed, with depression of the cutaneous surface, but new lesions continued to form. A purulent infection of the teeth, necessitating the extraction of fourteen teeth, was accompanied by a distinct increase in the number of new lesions and an elevation of temperature.

Hartwell and Thannhauser [21] reported the case of a 32 year old white woman whose lesions began on the shins and soon spread over the back, abdomen, breasts and neck. When first observed, she had, in addition to the nodules, acute pericarditis and pleural effusion. She had a temperature as high as 103 F. Crusting was present over two of the nodules. There was gradual improvement, and after six admissions to the hospital the patient had gained 43 pounds (19.5 Kg.). No evidence of cardiac change was present, and the nodules had healed, leaving depressed areas.

Ziegert [22] in September 1940 reported the case of a 34 year old woman with two palm-sized lesions on the chest and abdomen and smaller lesions in the left axilla and on the arms. Fever and leukopenia were present. The histologic observations reported conform to those made in other cases of this disease.

Hanson and Fowler [23] in 1941 reported the case of a 28 year old white man with recurring lesions on the right leg. Their patient showed slow healing of the wound made for removal of a biopsy specimen, as well as the unusual feature of spontaneous rupture of a lesion on the calf.

Pinetti, according to Baumgartner and Riva,[4] in 1941 reported the case of a 2 year old male baby who had lesions in the unusual locations of the head, the neck and the penis. Larson and Ootkin [24] reported the case of a 58 year old man who was observed with a number of painful nodules on the chest, the back, the thighs and the arms. The histologic picture was typical. The patient was observed for eight months, during which time there was no recurrence of the disease.

20. Skiold, N.: Relapsing Febrile Nonsuppurative Panniculitis, Acta med. Scandinav. **105**:43-47, 1940.

21. Hartwell, A. S., and Thannhauser, S. J.: Case Presentation and Discussion of Relapsing Febrile Nodular Nonsuppurative Panniculitis, Bull. New England M. Center **2**:362-369 (Dec.) 1940.

22. Ziegert, H. J.: Febrile Panniculitis (Weber-Christian Disease), Zentralbl. f. inn. Med. **61**:610-612 (Sept.) 1940.

23. Hanson, W. A., and Fowler, L. H.: Relapsing Febrile Nodular Nonsuppurative Panniculitis, Minnesota Med. **24**:779-782 (Sept.) 1941.

24. Larson, C. P., and Ootkin, B. N.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease): Case, Am. J. Clin. Path. **11**:781-787 (Oct.) 1941.

Two more cases were reported by Carol and associates [25] in 1941. Rosenberg and Cohen [26] added 2 more cases to the literature in 1942 and reported that in their cases they had been able to produce the lesions at will with either iodides or bromides once the syndrome had been established.

Miller and Kritzler [2c] in 1943 reported the first autopsy on a patient whose death had resulted from Weber-Christian disease. They were unable to find any specific lesions internally and gave as nonspecific lesions the accumulation of fat and focal necrosis of the liver, hydropic degeneration of the adrenal cortex cells and the presence of large numbers of red cells in the fixed members of the reticuloendothelial system. They emphasized the failure of the sulfonamide compounds (sulfadiazine, sulfathiazole and sulfanilamide) to have a favorable influence on the course of the disease. Their patient was a 34 year old Jewish housewife.

Larkin and associates [1] reviewed the literature in 1944 and added the case of a 2 year old male child with lesions of the feet and ankles, which were apparently asymptomatic with the exception of the fact that the patient had an undulating fever, with temperatures occasionally as high as 102 F. Spain and Toby [27] reported an interesting case in which the patient was admitted to the hospital and died one week later with uremia from the terminal stage of chronic glomerulonephritis. During this week nodules which were typical of Weber-Christian disease developed. A necropsy was performed, and, besides the expected observations of the effects of the glomerulonephritis, nodules of fat necrosis were found in the panniculus adiposus and in the omental, mesenteric and pretracheal fat deposits. This case, then, represented the first one in which specific internal lesions, as well as specific external lesions, were reported.

Baumgartner [28] reported the thirty-seventh case in 1944 and the thirty-eighth case [4] in 1945. Friedman [2b] reported the thirty-ninth case of the Weber-Christian syndrome in 1945 and was able to secure an autopsy on the patient. The primary cause of death was septicopyemia due to infection with Staphylococcus albus and Staph. aureus. The pathologic alterations in the viscera yielded no light as to the essential nature of the disease. Changes in the visceral adipose tissue, such as those described by Spain and Toby, were not seen. Focal lesions in

25. Carol, W. L.; Prakken, J. R., and van Zwijndregt, H. A., cited by Baumgartner and Riva.[4]

26. Rosenberg, W. A., and Cohen, T. M.: Relapsing Febrile Nodular Nonsuppurative Panniculitis, Illinois M. J. **81**:59-62 (Jan.) 1942.

27. Spain, D. M., and Toby, J. M.: Nonsuppurative Nodular Panniculitis (Weber-Christian Disease), Am. J. Path. **20**:783-787 (July) 1944.

28. Baumgartner, W.: Pathology of Adipose Tissue, Helvet. med. acta. **11**:155-159 (April) 1944.

the adrenal cortex similar to those noted in Miller and Kritzler's case were observed here.

Arnold [29] added a report of a case in 1945 in which he described the control of the disease by means of sulfapyridine after sulfathiazole, sulfadiazine and sulfanilamide had all failed. He stated that on discontinuance of treatment with sulfapyridine the symptoms would immediately reappear, although in each instance to a less degree, and that on resumption of administration of the drug the symptoms would promptly disappear. Arnold found a close correlation in his case between the clinical course and the erythrocyte sedimentation rate and the Weltmann coagulation reaction. His patient had five relapses and five remissions, according to whether sulfapyridine was given or not, and finally seemed to have attained a permanent remission without the drug.

In 1945 Ives [10b] added the forty-first case, one in which there was a definite antecedent history of an ulcer of the arm from a cigaret burn. Ungar [2d] recorded another death from the Weber-Christian syndrome, in a woman aged 37, who died nine months after the onset of her illness. Hers was one of the few reported cases in which there was a positive reaction to the serologic test for syphilis. It was interesting to note that potassium iodide therapy was attempted and produced an exacerbation of this patient's lesions. Ungar entitled his article "Relapsing Febrile Nodular Inflammation of Adipose Tissue," thus giving a hint of the manner in which his case differed from the usual picture presented. There was a pronounced tendency toward suppuration of the nodules, this manifestation rendering invalid the adjective "nonsuppurative," usually employed in describing the syndrome. Apparently the cause of death in this case was a hematogenous peritonitis, the infection (with hemolytic streptococci) having arisen from the tonsils, which contained abundant streptococcic abscesses. Ungar expressed the opinion that the nonsuppurative changes have no specific significance in the pathologic process of the Weber-Christian syndrome and that they are more likely to be due to tissue injury by fatty substances liberated in the course of destruction of fat cells by suppurative inflammation. Autopsy revealed granulomatous and suppurative involvement of both the panniculus adiposus and the adipose tissue in the thorax and the abdomen.

Zee [30] reported the forty-third case in 1946, that of a man aged 23 who was treated first with sulfadiazine, with no relief, and then with penicillin, with an apparent cure. Zee urged further trial of penicillin in the treatment of the syndrome.

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29. Arnold, H. L., Jr.: Nodular Nonsuppurative Panniculitis (Weber-Christian Disease): Preliminary Report of Case Controlled by Sulfapyridine (Sulfonamide), Arch. Dermat. & Syph. **61**:94-99 (Feb.) 1945.

30. Zee, M. L.: Nodular Nonsuppurative Panniculitis Treated with Penicillin, J. A. M. A. **130**:1219-1220 (April 27) 1946.

The following is the forty-fourth case to be reported; in this instance, the syndrome was secondary and incidental to the compliant for which the patient was admitted.

REPORT OF CASE

Mrs. A. J., aged 35, was admitted May 11, 1947, to Mt. Carmel Mercy Hospital, Detroit, to the surgical service of Dr. William Cassidy, with a complaint of tumor of the right breast. She was unsure of the duration, but she had discovered the growth three weeks before admission. She had had no pain in the breast at any time. In addition to her chief complaint, she stated that she had

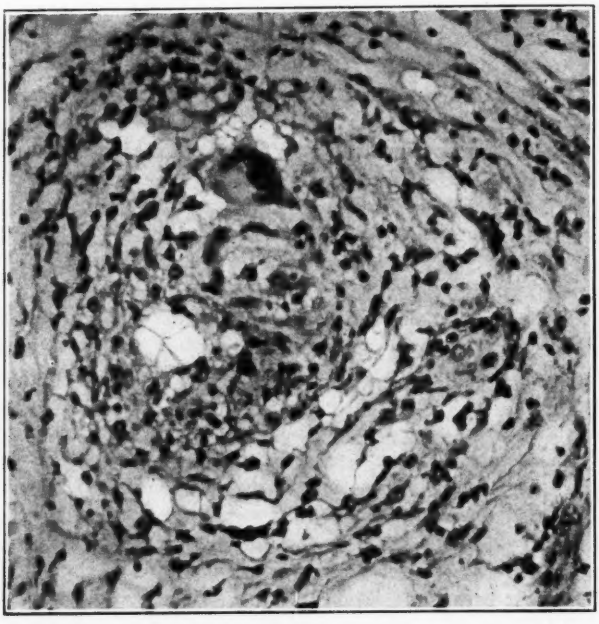

Fig. 1.—A solitary tubercle-like lesion composed of epithelioid-like cells arranged in a concentric or diffuse manner. A typical Langhans giant cell is seen in the upper part of the whorls of the tubercle-like lesion.

had multiple painful, bean-sized nodules on her arms and legs, some of which were still present. In the acute stage these lesions produced a purplish discoloration of the overlying skin, which finally changed to a brown and then faded nearly completely. The nodules were subcutaneous in origin and location, and ulceration had never occurred. The patient stated that she had been bothered with the condition for a three year period and that there was a tendency for the lesions to regress in the spring and summer. In winter, during an acute attack, the patient had been unable to walk because of swelling of the legs and pain. About two years before admission she had been admitted to another hospital and a biopsy of a nodule had been done. The biopsy at that time had revealed only

a chronic dermatitis. There were no operations or other serious illnesses in her past history. Her menstrual periods had been irregular for two and one-half months prior to admission to that hospital, having occurred every nineteen days. Before that they had been regular, having occurred every twenty-eight days with a duration of seven days. She had one child, full term, born about one month before her present admission. She had had a premature delivery at eight months, seventeen months before this admission, the child having lived two and one-half days.

Physical examination revealed a well developed and well nourished white woman, not acutely ill. The entire physical examination was noncontributory, with the following two exceptions: 1. The left breast showed no masses; the right breast revealed an irregular ill defined mass just deep to the nipple, mov-

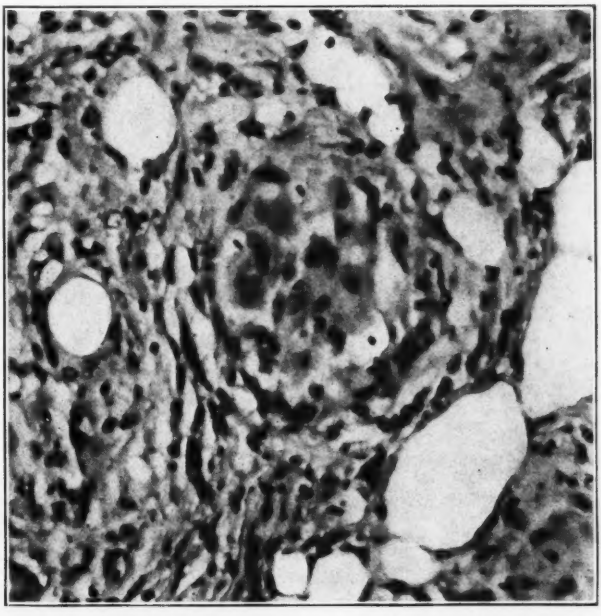

Fig. 2.—Several large foam cells, or macrophages ("lipophages").

able, firm, not attached to the skin or overlying fascia and possibly the size of a small lemon; no nodes were palpable in the axillas. 2. On the lower third of each leg there were subcutaneous nodules, about the size of olives, although considerably more flattened; these were firm, and slightly movable, with apparently normal overlying skin; several were present on each leg and were slightly tender.

A complete blood count revealed no abnormalities: hemoglobin, 13.4 Gm.; red blood cells, 4,220,000; white blood cells, 7,400; polymorphonuclear leukocytes, 52; lymphocytes, 35; monocytes, 5; basophils, 1, and stab cells, 7. Reactions to the Kahn test were negative, and urinalysis showed normal condition. Blood cholesterol was 183 mg. per hundred cubic centimeters. Tuberculin tests elicited nega-

tive reactions. The provisional diagnosis of the tumor in the breast was fibroadenoma or carcinoma, and the provisional diagnosis of the nodules on the legs was erythema nodosum.

On May 12, 1947, the patient was taken to the operating room, and, while she was under cyclopropane anesthesia, the mass in the right breast was excised. After this operation, one of the subcutaneous nodules from the lower third of each leg was excised and sent to the laboratory for examination. The patient made an uneventful recovery after the operation. Roentgenologic examination of the thorax revealed some infiltration of all markings, heaviest in the base of the right lung. Both paravertebral gutters were clear. There were no areas of consolida-

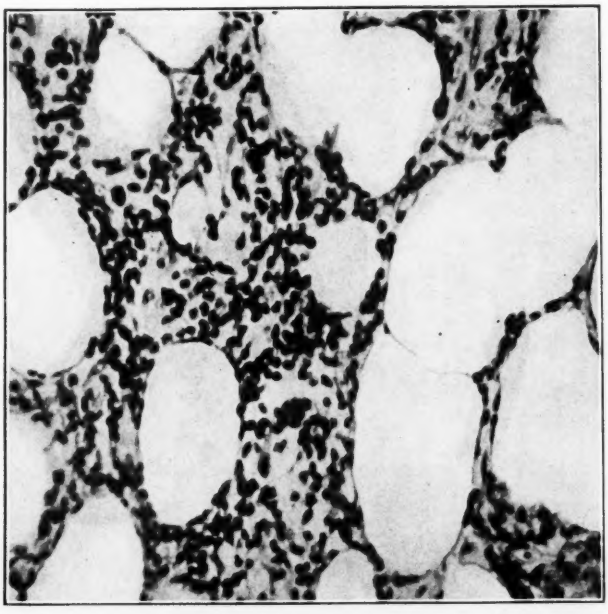

Fig. 3.—Cellular infiltration of the fat and connective tissue. Numerous small, oval clear spaces remain, corresponding to the remnants of the subcutaneous fat tissue which has not been infiltrated.

tion in either pulmonary field. There was no evidence of metastasis in either the lungs or the thoracic cage.

Dr. L. W. Gardner rendered the following pathologic report:

"*Gross Examination.*—1. The specimen (tumor of the breast) consisted of a round fragment of tissue measuring 5.5 cm. in diameter and 1.5 cm. in thickness. The tissue was pinkish gray and somewhat rough but glistening. The tumor was firm, nonfriable and definitely rubbery. Cross sections revealed a homogeneous yellowish white fibrous surface which did not grate when cut.

"2. In addition, there was an oval mass of tissue measuring 2.5 by 1 cm. One surface had attached to it an elliptic fragment of skin. Also, there was a mass

of tissue, measuring 2 by 0.6 cm., composed of a moderate amount of finely lobular grayish white fat. Serial sections revealed a pale, dull, homogeneous, grayish white surface. The tissue submitted was firm, nonfriable, definitely rubbery, lobular and grayish white.

"*Microscopic Examination.*—1. Sections revealed chronic cystic mastitis; no malignant changes.

"2. Sections consisted of a cutaneous biopsy specimen, partially covered on one side by squamous epithelium showing no evidence of epithelial changes, and a small subcutaneous nodule. The upper portion of the cutis was essentially normal. A slight lymphocytic infiltration in the perivascular space was noted in the lower portion of the cutis. The chief pathologic changes were noted in the subcutis and adjoining fat in the form of a proliferative atrophy of the fatty

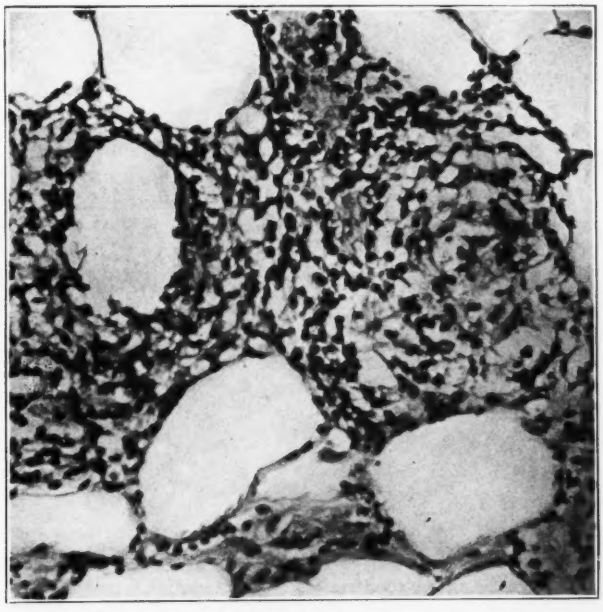

Fig. 4.—Rather dense inflammatory infiltration by lymphocytes, monocytes and plasma cells.

tissue. The latter contained numerous solitary and coalescing tubercle-like lesions composed of slightly acidophilic, epithelioid-like lesions arranged in a concentric or diffuse manner (fig. 1). A few large foam cells were noted in some areas (fig. 2). A sprinkling of small lymphocytes could be found in some of the sections. Numerous giant cells, some being typical Langhans cells, were noted (fig. 1). An occasional Touton cell could be identified. Apparently some of the lesions were centered around small capillaries, but there was no evidence of intimal proliferation or medial thickening. No evidence of caseation was seen. Between and within these lesions, numerous small oval or round clear spaces corresponded to the remains of subcutaneous fat which had not been infiltrated (fig. 3)."

In some sections there was rather dense inflammatory infiltration (fig. 4). Beginning fibrosis with gradual invasion by young connective tissue was noted in some sections (fig. 5). Special stains for fat revealed the presence of fat within the macrophages. The lobular arrangement of the fat appeared to limit partially the process of infiltration and proliferation. Stains for acid-fast organisms were negative.

The patient, in good condition, was discharged from the hospital on May 16, 1947, the final diagnoses being as follows: (1) chronic cystic mastitis, no malignant characteristics, and (2) relapsing febrile nodular panniculitis (Weber-Christian disease), no malignant characteristics.

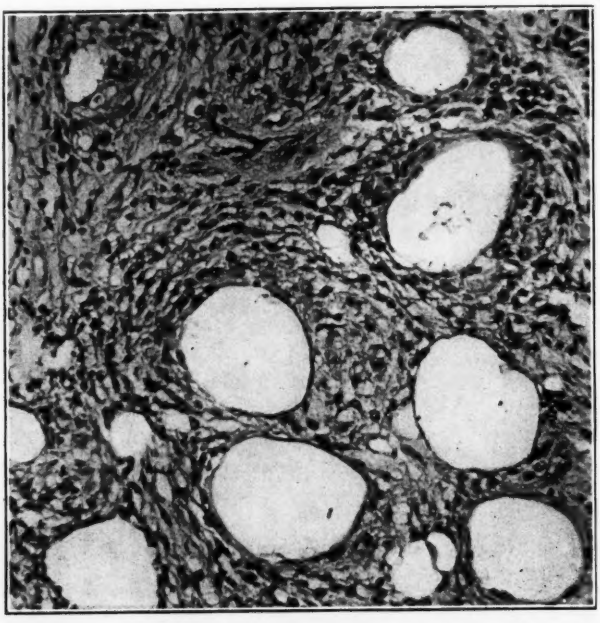

Fig. 5.—Large fat spaces resulting from coalescence of necrotic fat cells, with beginning infiltration of the inflammatory area and replacement by fibrotic tissue.

The outcome in the 44 previously reported cases, then, has been as follows:

Six deaths have been reported in connection with the syndrome. In Bailey's case the patient died apparently as a result of the syndrome, but no autopsy was permitted. In Tilden's case the patient died from tuberculosis after having apparently been cured of the disease, the autopsy having revealed no lesions attributable to the Weber-Christian syndrome. The first death from the Weber-Christian syndrome with autopsy reported was that of Miller, who likewise was unable to find any specific internal lesions. The patient in Spain and Toby's case died

from glomerulonephritis shortly after acquiring panniculitis, and nodules of fat necrosis were found in the pretracheal, omental and mesenteric fat as well as in the panniculus adiposus. In Friedman's case a staphylococcic septicopyemia was the true cause of death, although the death was attributed to panniculitis. In Ungar's case the patients died from streptococcic peritonitis hematogenously spread from the tonsils. It is interesting to speculate that possibly the tonsils were the source also of the panniculitis, and this would further reinforce the idea that Weber-Christian disease is not the cause but rather the effect of some distant infection. This theory will be discussed further when the etiology is considered. In the other 38 cases in the literature, the course seems to have been one of chronicity with frequent relapses. In the few cases in which the disease appeared to have been permanently arrested the patients were not observed long enough to warrant the conclusion; a possible exception was Gilchrist and Ketron's case, which was reported without a recurrence as late as 1943,[2c] having been first reported in 1916.

A review of the laboratory data collected on the 44 cases reveals nothing significant (see table 2). A leukocyte count below 5,000 was noted in 8 cases, one above 15,000 in 3, moderate leukocytosis in 4 and a normal leukocyte count in others. A red blood cell count below 4,000,000 was found in 8 cases, none of a severe form of the disease. Moderate eosinophilia and relative lymphocytosis were noted in a few cases. Sternal marrow was normal in 3 cases, as were total blood lipids in 2 cases. The blood cholesterol was moderately elevated in 1 case[1] and considerably elevated in 1 other.[2b] In the 14 others reported there was no deviation from normal, an important point to be considered later in discussion of the etiology. The amount of cholesterol ester was normal, with the exception that it fell from normal to 10 per cent in Miller's case as death approached, this manifestation indicating hepatic damage. The proportion of serum phosphatase was elevated slightly in 2 cases and was normal in 2 others. Amounts of inorganic phosphorus, sugar, urea nitrogen, calcium, chlorides, bromides and uric acid in the serum were all normal. The ratio of nonprotein nitrogen was elevated severely in Spain's case, in which the patient died from uremia. Plasma proteins were not remarkable in variation from the normal range. Cultures of the blood were negative, and cultures, smears and inoculations of material from nodules produced no organisms in 21 cases; in 1 case[15] only were blood cultures and nodule cultures positive for staphylococci, and I list this case as one of the 2 not particularly well authenticated. Blood agglutination tests for Brucella melitensis, the paratyphoid bacillus, Eberthella typhosa, the typhus organism, Pasteurella tularensis and hemolytic streptococci all had negative results. The erythrocyte sedimentation rate appeared to be elevated moderately in

TABLE 1.—*Summary of Forty-Four Cases of the Weber-Christian Syndrome Reported*

Case No.	Author	Duration, Yr.	Year	Age, Yr.	Sex	Pain	Fever	Distribution of Lesions: Arms	Abdomen	Back	Thighs	Legs
1	Pfeifer [5]	2	1892	23	F	—	+	+	+	+	+	+
2	Gilchrist and Ketron [6]	½	1916	8	F	—	+	—	—	—	+	+
3	Weber [7]	1/10	1925	50	F	+	+	+	—	+	+	+
4	Christian [8]	10	1928	25	F	—	+	+	+	+	—	+
5	Netherton [12]	1	1933	46	F	+	+	—	—	—	—	+
6	Alderson and Way [11]	15	1933	41	F	+	+	+	—	—	+	+
7	Weber [9b]	1/12	1935	53	M	+	+	+	—	—	+	+
8	Brill [13]	3	1936	19	F	+	+	+	+	—	+	—
9	Bailey [14*]	⅓	1937	24	F	+	+	+	+	+	+	—
10	Bailey [14]	¾	1937	43	F	—	+	+	+	—	+	—
11	Bailey [14]	¾	1937	56	F	+	+	—	+	—	+	+
12	Bailey [14]	4	1937	38	M	—	+	+	—	—	+	+
13	Bailey [14]	10	1937	45	F	—	+	+	+	—	+	+
14	Reed and Anderson [15]	9	1937	34	F	+	—	—	—	—	+	+
15	Cummins and Lever [16]	⅙	1938	10	F	—	+	+	—	—	—	—
16	Cummins and Lever [16]	½	1938	10	F	+	+	—	—	—	+	+
17	Shaffer [10c]	12	1938	33	F	—	+	+	?	?	+	+
18	Puente [3b]	2½	1938	48	F	+	+	—	—	+	—	—
19	Binkley [10a]	⅙	1939	36	F	—	—	+	—	—	—	+
20	Mengoli [17]	½	1939	12	M	+	+	+	—	+	+	+
21	Hazel and Lamb [18]	1	1940	11	F	—	—	—	+	—	+	+
22	Tilden, Gotshalk and Avakian [19†]	1/12	1940	64	M	+	+	+	+	+	+	+
23	Tilden, Gotshalk and Avakian [19]	1/12	1940	54	F	+	+	—	+	—	+	—
24	Skiold [20]	4	1940	51	F	+	+	+	—	—	+	+
25	Hartwell and Thannhauser [21]	2	1940	32	F	—	+	+	+	+	—	+
26	Ziegert [22]	?	1940	34	F	+	+	+	+	+	—	—
27	Hanson and Fowler [23]	¼	1941	28	M	+	+	—	—	—	—	+
28	Pinetti [3a]	?	1941	2	M	?	+	+	—	—	+	+
29	Larson and Ootkin [24]	1/12	1941	58	M	+	+	+	+	+	+	—
30	Carol, Prakken and van Zwijndregt [25]	?	1941	35	F	?	?	+	—	—	—	+
31	Carol, Prakken and van Zwijndregt [25]	?	1941	½	F	?	+	+	+	—	+	+
32	Rosenberg and Cohen [26]	1/12	1942	38	F	+	+	—	—	—	—	+
33	Rosenberg and Cohen [26]	1/30	1942	35	F	+	—	—	—	—	—	+
34	Miller and Kritzler [2c‡]	5/12	1943	34	F	+	+	+	—	+	+	+
35	Larkin, DeSanctis and Margulis [1]	¼	1944	2	M	—	+	—	—	—	—	+
36	Spain and Toby [27§]	1/365	1944	51	M	+	+	+	—	—	—	+
37	Baumgartner [28]	10	1944	40	F	+	+	+	—	+	+	+
38	Baumgartner [28]	8	1945	56	F	+	+	+	+	+	+	+
39	Friedman [2b‖]	1	1945	23	F	+	+	—	—	—	+	+
40	Arnold [29]	⅙	1945	27	F	+	+	+	—	+	+	+
41	Ives [10b]	1/24	1945	53	M	—	+	+	—	—	+	—
42	Ungar [30¶]	1/12	1946	37	F	+	+	+	+	+	+	+
43	Zee [30]	1/12	1946	23	F	—	+	+	+	+	+	+
44	Bendel	1/12	1948	35	F	+	—	+	—	—	—	+

* Death apparently from Weber-Christian disease. No autopsy.
† Death from tuberculosis, apparent cure of Weber-Christian disease. Autopsy.
‡ Death from Weber-Christian disease. First reported autopsy.
§ Death
‖ Death
¶ Death

Reported in the Literature (Modified from Larkin, DeSanctis and Margulis[1])

Lesions					
Legs	Other Parts	Secondary Atrophy	Local or Systemic Infections	Drugs	Remarks
+	.....	+	Syphilis	.....	
+	.....	+	.....	.....	
+	.....	—	Dental caries	Bromides	
+	.....	+	.....	.....	
+	.....	+	Tonsillectomy four years before	Quinine, salicylates	
+	.....	+	Dental caries	.....	
+	.....	—	Syphilis	Iodides caused exacerbation	Pus in nodules
—	.....	+	Tonsillitis, dental caries	.....	
—	.....	+	Tonsillitis, dental caries	Iodides (?)	
—	.....	+	Tonsillitis, dental caries	Iodides	
+	.....	+	Tonsillitis, dental caries	Bromides	
+	.....	+	Tonsillitis	Bromides	
+	.....	+	Tonsillitis, dental caries	Iodides caused exacerbation	
+	.....	+	.....	.....	
—	.....	+	Dental caries	.....	
+	Feet	+	Dental caries	.....	
+	.....	+	Tonsillitis, dental caries (?)	.....	Liquefaction in nodules
—	Breast	+	Staphylococci cultured in blood, tuberculosis (?)	.....	Staphylococci in nodules
+	Breast	+	Tonsillitis, dental caries	.....	Liquefaction in nodules
+	Hands, face	+	Patient convalescing from typhus	.....	
+	.....	+	.....	.....	
+	.....	+	Tuberculosis, avitaminosis	.....	
—	.....	+	Dental caries	.....	
+	.....	+	Dental caries	.....	Endomyocarditis
+	Face	+	Pleurisy, pericarditis	.....	
—	Breast	?	Abortion previously (?)	.....	
+	.....	+	.....	.....	
+	Head, neck, penis	?	.....	.....	
—	Chest	+	.....	.....	
+	Shoulder	—	Possible tuberculosis	.....	
+	.....	—	Hydrocephalus	.....	
+	.....	—	Prolonged diet for gallbladder disease	Iodides, bromides precipitated lesions after syndrome established	
+	.....	+	Dental caries	.....	
+	Buttocks	+	Extractions of infected teeth	Sulfonamide therapy	
+	Feet	+	.....	.....	
+	Visceral nodules	—	Chronic glomerulonephritis	.....	
+	Buttocks	—	Tonsillitis	.....	
+	Buttocks	—	Tonsillitis	.....	Mitral insufficiency
+	Breast, buttocks	+	Extraction of infected tooth	.....	Splenomegaly
+	Chest	?	.....	Sulfapyridine therapy	
—	.....	+	Ulcer on arm from burn	.....	Spontaneous rupture of nodules
+	Viscera involved	—	Syphilis, streptococcic tonsillitis	Iodides caused exacerbation	Pus in nodules
+	.....	?	Previous war wounds	Penicillin therapy	
+	.....	—	.....	.....	Cystic mastopathy

§ Death from chronic glomerulonephritis, Weber-Christian disease at death. Autopsy.
‖ Death from Weber-Christian disease. Septicemia, with Staph. albus and Staph. aureus. Autopsy.
¶ Death from Weber-Christian disease. Peritonitis, with hemolytic streptococci. Autopsy.

TABLE 2.—*Review of the Laboratory Data on Forty-Four Cases of the W*

Case No.	Author	Year	Age, Yr.	Blood Count: Red Blood Cells (Millions)	Blood Count: White Blood Cells	Blood Count: Differential	Blood Count: Hemoglobin	Sternal Marrow	Lipids, Mg./100 Cc.	Cholesterol, Mg./100 Cc.	Cholesterol Ester, Mg./100 Cc.
1	Pfeifer [5]	1892	23	4.1	Normal	Normal	85%	.....	.....	.....	.....
2	Gilchrist and Ketron [6]	1916	8	...	15,600	Polymorphonuclear cells	.....	.....	.....	Normal	.....
3	Weber [7]	1925	50	4.4	10,500	Normal	85%	.....	.....	.....	.....
4	Christian [8]	1928	25	4.9	3,000	Normal	85%	.....	.....	.....	.....
5	Netherton [12]	1933	46	5.0	6,900	Normal	72%	.....	.....	.....	.....
6	Alderson and Way [13]	1933	41	...	.....	.....	.....	.....	.....	.....	.....
7	Weber [9b]	1935	53	...	.....	.....	.....	.....	.....	.....	.....
8	Brill [13]	1936	19	...	Leukopenia	Lymphocytes	.....	Normal	.....	220	.....
9	Bailey [14]	1937	24	3.9	5,100	.....	54.6%	.....	.....	.....	.....
10	Bailey [14]	1937	43	4.6	6,900	.....	69%	.....	.....	.....	.....
11	Bailey [14]	1937	56	...	.....	.....	.....	.....	.....	.....	.....
12	Bailey [14]	1937	38	...	.....	.....	.....	.....	.....	.....	.....
13	Bailey [14]	1937	45	Normal	Normal	Normal	Normal	.....	.....	.....	.....
14	Reed and Anderson [15]	1937	34	4.3	6,600	Normal	90%	.....	.....	.....	.....
15	Cummins and Lever [16]	1938	10	Normal	Normal	Normal	Normal	.....	Normal	Normal	Normal
16	Cummins and Lever [16]	1938	10	Normal	11,500	Normal	Normal	.....	.....	.....	.....
17	Shaffer [10c]	1938	33	Normal	4,000	Normal	.....	.....	.....	125-215	.....
18	Puente [3b]	1938	48	Anemia	5,800	Lymphocytes	.....	.....	.....	.....	.....
19	Binkley [10a]	1939	36	4.4	13,000	Normal	85%	.....	644	190	122
20	Mengoli [17]	1939	12	...	.....	.....	.....	.....	.....	.....	.....
21	Hazel and Lamb [18]	1940	11	4.5	16,800	4% Eosinophils	.....	.....	.....	190	.....
22	Tilden, Gotshalk and Avakian [19]	1940	64	3.3	6,800	Normal	50%	Normal	.....	177	.....
23	Tilden, Gotshalk and Avakian [19]	1940	54	3.7	.....	.....	56%	.....	.....	181	.....
24	Skiold [20]	1940	51	4.3	3,100	5% Eosinophils	90%	.....	.....	.....	.....
25	Hartwell and Thannhauser [21]	1940	32	...	.....	.....	.....	.....	.....	.....	.....
26	Ziegert [22]	1940	34	Anemia	3,300	.....	.....	.....	.....	.....	.....
27	Hanson and Fowler [23]	1941	28	Normal	Normal	.....	89%	.....	.....	166.8	.....
28	Pinetti [8a]	1941	2	Normal	Normal	Normal	Normal	.....	.....	.....	.....
29	Larson and Ootkin [24]	1941	58	Normal	Normal	Normal	Normal	.....	.....	.....	.....
30	Carol, Prakken and van Zwijndregt [25]	1941	35	...	.....	.....	.....	.....	.....	.....	.....
31	Carol, Prakken and van Zwijndregt [25]	1941	½	...	.....	.....	.....	.....	.....	.....	.....
32	Rosenberg and Cohen [26]	1942	38	4.4	8,650	Normal	13.2 Gm.	.....	.....	234	.....
33	Rosenberg and Cohen [26]	1942	35	4.1	5,750	.....	12.4 Gm.	.....	.....	216	.....
34	Miller and Kritzler [2c]	1943	34	Normal	Normal	Normal	Normal	.....	.....	186	Normal to 10%
35	Larkin, DeSanctis and Margulis [1]	1944	2	4.3	6,900	5% Eosinophils	11 Gm.	.....	.....	271	145
36	Spain and Toby [27]	1944	51	3.5	8,500	Polymorphonuclear cells	8.5 Gm.	.....	.....	.....	.....
37	Baumgartner [28]	1944	40	...	Normal	4% Eosinophils	.....	.....	.....	.....	.....
38	Baumgartner [28]	1945	56	4.6	5,300	5% Eosinophils	83%	.....	.....	.....	.....
39	Friedman [3b]	1945	23	3.7	Leukopenia	Stab cells	11 Gm.	Moderately cellular	.....	198	.....
40	Arnold [29]	1945	27	...	12,100	Eosinophils	.....	.....	.....	180	.....
41	Ives [10b]	1945	53	Normal	1,000	Normal	.....	.....	.....	.....	.....
42	Ungar [2d]	1946	37	Anemia	18,000	.....	.....	.....	.....	.....	.....
43	Zee [30]	1946	23	...	3,200	.....	.....	.....	.....	.....	.....
44	Bendel	1948	35	4.2	7,400	Normal	13.4 Gm.	.....	.....	192	.....

the Weber-Christian Syndrome Reported in the Literature

	Blood															
Cholesterol Ester, Mg./ 100 Cc.	Iodine Number	Serum Phosphatase, Mg./ 100 Cc.	Serum Inorganic Phosphorus, Mg./ 100 Cc.	Sugar, Mg./ 100 Cc.	Urea Nitrogen, Mg./ 100 Cc.	Nonprotein Nitrogen, Mg./ 100 Cc.	Calcium, Mg./ 100 Cc.	Chlorides, Mg./ 100 Cc.	Bromides, Mg./ 100 Cc.	Uric Acid, Mg./ 100 Cc.	Plasma Protein, Gm./ 100 Cc.	Albumin, Gm./ 100 Cc.	Globulin, Gm./ 100 Cc.	Culture of Blood	Erythrocyte Sedimentation Rate
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	....	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	....	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	—	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	—	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	—	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	....	....
.....	.....	.....	4.2	106	....	....	....	....	....	....	....	....	....	—	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	—	17 mm./ hr.
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	....	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	—	....
.....	.....	.....	.....	....	....	....	....	....	Normal	....	....	....	....	—	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	—	....
.....	.....	.....	.....	....	....	....	10.9	....	....	....	....	....	....	....	....
Normal	Normal	Normal	Normal	....	....	Normal	Normal	Normal	....	....	....	....	....	....	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	....	....
.....	.....	.....	.....	75-85	12	....	....	....	....	....	....	....	....	—	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	Staph. aureus	....
139	122	.....	.....	83.8	....	....	....	....	....	....	....	....	....	....	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	—	....
190	.....	.....	.....	96	....	....	....	....	....	....	....	....	....	....	....
117	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	—	....
181	.....	.....	.....	89	....	40	....	....	....	....	....	....	....	—	Normal
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	—	36 mm./ hr.
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	....	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	....	....
164.4	.....	.....	.....	87.5	....	....	....	....	....	....	....	....	....	....	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	....	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	....	....
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	—	20 mm./ hr.
.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	—	....
234	.....	.....	3.2	124	9.4	....	....	....	....	4.1	....	....	....	....	....
216	.....	.....	4.26	76.5	13.5	....	10.5	490	Less than 75	2.68	....	....	....	....	....
166	Normal to 10%	Normal	6.6 Bodansky units	Normal	....	....	Normal	10.3	500	Less than 75	....	Normal to 6.2	2.4	2.7	—	Normal
275	145	.....	.....	.....	....	20	39.5	....	....	Normal	....	....	....	....	....	15 mm./ hr.
.....	.....	.....	4.3 Bodansky units	.....	....	....	272	....	....	....	....	6.1	4.1	2.0	....	....
.....	.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	—	60 mm./ hr.
.....	.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	—	58/86
188	.....	.....	6.7 Bodansky units	3.9	82-88	21	....	....	....	....	....	5.2-5.7	....	....	....	10 mm./ hr.
180	.....	.....	.....	.....	....	....	....	8.3	....	....	....	7.3	....	....	....	Parallel to clinical course
.....	.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	—	....
.....	.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	—	....
.....	.....	.....	.....	.....	....	....	....	....	....	....	....	....	....	—	21 mm./ hr.
183	.....	.....	.....	....	....	....	....	....	....	....	....	....	....	....	....

(Table continued on next page)

TABLE 2.—*Review of the Laboratory Data on Forty-Four Cases of the Webe*

Case No. (Continued)	Blood Agglutination Tests									Smear, Culture, Inoculation of Material from Lesions	Liver Function Tests	Spinal Fluid	Urin
	Weltmann Coagulation Band	Br. Melitensis	Paratyphoid Bacillus	E. Typhosa	Typhus Organism	Past. Tularensis	Str. Hemolyticus A.	Tuberculin Test	Blood Serology				
1	....	....	....	....	....	....	....	....	+	—	.....	..	..
2	....	....	....	....	....	....	....	—	....	.....	.....	..	—
3	....	....	....	....	....	....	....	1+	....	.....	.....	..	..
4	....	—	....	....	....	....	....	....	—	—	.....	..	—
5	....	—	....	....	....	....	....	....	—	—	.....	—	..
6	....	—	....	....	....	....	....	4+ 2d test	....	.....	.....	..	..
7	....	....	....	....	....	....	....	....	+	.....	.....	..	..
8	....	—	—	—	....	....	....	....	—	—	.....	..	..
9	....	—	—	—	....	—	....	—	—	— for tuberculosis, lepra	—	..	—
10	....	....	....	....	....	....	....	....	—	.....	.....	..	..
11	....	....	....	....	....	....	....	....	....	.....	.....	..	..
12	....	....	....	....	....	....	....	....	—	.....	.....	..	..
13	....	....	....	....	....	....	....	—	—	.....	.....	..	—
14	....	—	....	....	....	—	....	....	—	—	.....	..	—
15	....	....	....	....	....	....	....	....	....	—	.....	..	..
16	....	....	....	....	....	....	....	—	....	—	.....	..	..
17	....	....	....	....	....	....	....	+	—	—	.....	..	—
18	....	....	....	....	....	....	....	+	....	Staph. aureus	.....	..	
19	....	—	—	—	—	....	....	....	—	— for tuberculosis	.....	..	—
20	....	....	....	....	....	....	....	—	....	—	.....		
21	....	....	....	....	....	....	....	....	—	.....	.....	..	..
22	....	....	....	—	—	....	....	....	—	— for lepra on skin	.....	..	—
												..	3+ albumi
23	....	....	....	....	....	....	....	—	....	— for lepra on skin	.....	..	—
24	....	....	....	....	....	....	....	....	—	.....	.....		
25	....	....	....	....	....	....	....	....	....	.....	.....	..	—
26	....	....	....	....	....	....	....	....	—	.....	.....	..	..
27	....	....	....	....	....	....	....	—	—	—	.....	..	..
28	....	....	....	....	....	....	....	—	—	.....	.....	..	—
29	....	....	....	....	....	....	....	....	—	—	.....	..	..
30	....	....	....	....	....	....	....	?	—	.....	.....	..	—
31	....	....	....	....	....	....	....	—	—	—	.....	..	..
32	....	....	....	....	....	....	....	....	—	.....	.....	..	..
33	....	....	....	....	....	....	....	....	—	.....	.....	..	—
34	....	—	....	....	....	....	—	—	—	—	3+ Cephalin flocculation	..	— 1+ albumi
35	....	....	....	....	....	....	....	—	—	—	.....		
36	....	—	—	—	....	....	....	....	—	.....	2+ Cephalin flocculation	—	— 2+ albumi
37	....	....	....	....	....	....	....	....	....	—	.....		
38	....	....	....	....	....	....	....	....	—	.....	.....	..	..
39	....	—	—	—	....	....	....	—	....	—	.....	..	..
40	Left to 0	....	....	....	....	....	....	—	—	.....	.....	..	..
												..	—
41	....	....	....	....	....	....	....	....	....	.....	.....		
42	....	....	....	....	....	....	....	—	+	—	.....	..	..
43	....	—	—	—	....	....	....	....	....	.....	.....	..	..
44	....	....	....	....	....	....	....	—	—	.....	.....	..	—

the Weber-Christian Syndrome Reported in the Literature—Continued

Spinal Fluid	Urine	Basal Metabolic Rate	Miscellaneous Tests	Roentgenograms
..	..	.....	.....	
..	—	.....	.....	
..	..	.....	Normal findings in gastric analysis	Slight gastroptosis; possible "slight hilar tuberculosis"
..	—	— 2%	.....	
—	..	—11%	.....	
..	..	— 3%	.....	Thorax normal
..	..	.....	.....	
..	..	.....	.....	
..	—	.....	.....	Thorax normal; two areas of periapical infection (dental)
..	..	.....	.....	Thorax normal
..	..	.....	.....	Normal findings except for cholelithiasis and poorly functioning gallbladder
..	..	.....	.....	
..	—	.....	.....	Thorax normal
..	—	.....	Negative results in Frei test	Thorax normal
..	..	.....	Fatty acids in blood normal	Thorax and bones normal
..	..	.....	.....	Legs normal
..	—	—11%	Urinalysis normal, patch tests negative for halogens	Sinuses, pelvis, sacrum, teeth, skull, thorax and spinal cord normal; moderate splenomegaly
..	..	.....	.....	
..	—	.....	.....	
..	..	.....	.....	
..	—	—19%	.....	
..	3+ albumin	.....	.....	Thorax, long bones, gastrointestinal tract and skull normal; periapical abscesses (dental)
..	—	.....	.....	Thorax normal; periapical abscesses (dental)
..	—	.....	.....	
..	..	.....	.....	
..	..	.....	.....	
..	—	.....	Blood lipase normal	Thorax and right lower extremity normal
..	..	.....	.....	
..	—	.....	.....	
..	..	.....	.....	
..	—	+ 3%	.....	Nonfilling gallbladder
..	—	—15%	.....	
..	1+ albumin	— 5%	.....	Sinuses, thorax and right thigh normal
..	—	.....	.....	Ankles and feet normal
—	2+ albumin	.....	Melena, skin negative for trichinella	Thorax and abdomen normal
..	..	.....	.....	
..	..	.....	.....	Heart enlarged; mitral type insufficiency
..	..	.....	Test of skin with coccidioidin, 4+	Heart enlarged
..	—	.....	.....	Sinuses and thorax normal
..	..	.....	.....	
..	..	.....	.....	Thorax, sella turcica normal; splenomegaly revealed by abdominal flat plate
..	—	.....	.....	Thorax normal

4 cases and appreciably in 3; it closely paralleled the clinical course in 1.[29] In the last-mentioned case also the Weltmann coagulation band was found to conform to the state of the patient. The Weltmann test was not used in any of the other reported cases. Reactions to the tuberculin test were negative in 15 cases and positive in 4 others. Reactions to serologic tests of the blood were positive in 3 cases and negative in 27. Urinalysis was normal except in 3 of the fatal cases, in which it revealed albumin (1 to 3 plus). The basal metabolic rate was slightly low in the majority of the cases in which it was taken. Roentgenograms of the thorax, the long bones, the sinuses, the skull and the pelvis were normal, with the exception that cardiomegaly was revealed in 2 cases. In 3 cases there was periapical dental abscess, and in 2 roentgenologic examination showed splenomegaly. Laboratory procedures, such as tests for blood lipase and for fatty acids, the Frei test, gastric analysis, patch test with halogens and cutaneous tests with trichinella larvae all gave normal findings. In Friedman's case there were repeatedly positive reactions to cutaneous testing with coccidioidin, and healed lesions of coccidioidomycosis were found at autopsy. Review of these numerous laboratory tests reveals that they shed no light on the causation or, with the possible exception of the erythrocyte sedimentation rate and the Weltmann coagulation reaction, on the course of the disease, nor do they establish diagnostic criteria.

The pathologic picture has not been specific and has varied to some degree in most of the cases described. The usual gross appearance is that of small subcutaneous nodules, usually on the thighs or legs at first, which may or may not be tender, which frequently show no disturbance of the overlying skin but may exhibit ecchymosis and even occasionally ulceration and which are usually ill defined and almost fluctuant. These may coalesce to form large nodules. On healing, there is usually a depressed area, which is permanent and corresponds in depth to the thickness of the panniculus. Microscopically, the epithelium is usually little altered. The corium may show edema and increased vascularity.[16] In early lesions lipolytic histiocytes (macrophages) derived from the cells of reacting tissue [6] appear in the fat spaces and produce a foam cell appearance by the ingestion of fine droplets of the fat, which appears to have been altered so that it behaves as a foreign body, calling forth a foreign body response. Between the fat spaces, lymphocytic infiltration is seen. As time goes on, the foam cells regress and the nuclei tend to fuse, this development giving the cells the appearance of giant cells. As this activity is taking place, the stroma becomes more densely infiltrated with lymphocytes and mononuclear cells, which obliterate the empty fat spaces in many places. An interesting early finding may be the swelling and thrombosis of the smaller blood vessels.[19] The larger arterioles may show edema of the muscularis, with divided endothelial proliferation. Around the larger

venules definite lymphocytic infiltration is seen. The changes are seen early and persist in the older lesions. The last stage would appear to be fibrosis, with healing. Ungar expressed disagreement with this classic description in part and said that histologically the initial lesion is distinguished by leukocytic stasis in the blood capillaries and focal suppurative inflammation in the adipose tissue. These manifestations are followed by the development of granuloma-like lesions, which arise on the axis of the fibrous septums; the process terminates in scar-like formation, or foci or foamy cell alteration. Shaffer [10c] stated that the last-mentioned process results in liquefaction, as demonstrated by the loss of outline of the foam cells, with development of an amorphous foamy matrix in which the vesicular nuclei as well as the inflammatory round and polymorphonuclear cells are suspended.

As was stated previously, the pathologic picture is not specific, and similar pathologic changes resulting from actual trauma [31] or the injection of oily and other foreign substances, bacterial and nonbacterial [32]—particularly of insulin [32f] and recently even of various physiologic solutions [33]—have been seen. Friedman mentioned a case of "cold allergy" in which the application of ice to the forearm gave a histologic picture indistinguishable from the Weber-Christian syndrome.[34]

All the cases of the Weber-Christian syndrome have one major feature in common—involvement of subcutaneous or visceral fat alone—but this feature may also be found in other conditions, in which it plays a minor role; Weber and Gray [35] reported a case in which there were inflammatory changes in the muscle as well as in the subcutaneous fat and which they therefore called an instance of "polydermatomyositis." Clerici [36] and Stockman [37] discussed the relationship of chronic muscular

31. (*a*) Adair, F. E., cited by Binkley.[10a] (*b*) Berner, O., cited by Bailey.[2a] (*c*) Binkley.[10a] (*d*) Heyde, M., cited by Bailey.[2a]

32. (*a*) Alderson and Way.[11] (*b*) Duran-Reynals, F.: A. Necrotizing Disease in Rabbits Affecting Fatty and Muscular Tissues: Analogies with Weber-Christian Disease of Humans, Yale J. Biol. & Med. **18**:583-594 (July) 1946. (*c*) Eeg-Olofsson, R., cited by Rowe and Garrison.[32f] (*d*) Harbitz, H. J., cited by Bailey.[2a] (*e*) Lux, L., cited by Bailey.[2a] (*f*) Rowe, A. H., and Garrison, O. H.: Lipodystrophy: Atrophy and Tumefaction of Subcutaneous Tissue Due to Insulin Injections, J. A. M. A. **99**:16-18 (July 2) 1932.

33. (*a*) Netherton.[12] (*b*) Schwarzmann, J. M., cited by Bailey.[2a]

34. Keil, G. J., and Fromer, J., cited by Friedman.[2b]

35. Weber, F. P., and Gray, A. M. H.: Chronic Relapsing Polydermatomyositis with Predominant Involvement of the Subcutaneous Fat (Panniculitis), Brit. J. Dermat. **36**:544-560 (Dec.) 1924.

36. Clerici, A.: Chronic Muscular Rheumatism and Panniculitis, Gazz. d. osp. **49**:585-587 (May 13) 1928.

37. (*a*) Stockman, R.: British Medical Association Lectures on Chronic Muscular Rheumatism and Panniculitis, Brit. M. J. **1**:293-295 (Feb.) 1928; (*b*) Causation of Fibrositis and Panniculitis, M. J. & Rec. **128**:466-467 (Nov. 7) 1928.

rheumatism and panniculitis, and Keil[38] attempted to classify panniculitis.

The etiology of this disease is in doubt. A survey of table 1 reveals that patients in 34 of the cases were female and 10 were male, a ratio of over 3 to 1. The patients in only 9 of the cases were under the age of 20, and only 3 of them were infants. The syndrome appears to affect predominantly persons who are middle aged, with several patients being elderly. One interesting hypothesis advanced as to etiology is that the disorder represents in adults the same disease as subcutaneous fat necrosis does in the newborn.[39] In the latter condition it is generally assumed that obstetric trauma, acting on the fat with a high melting point which is present in the newborn infant, is responsible for the condition. Chemical analysis of the subcutaneous fat in the newborn child reveals that only 65 per cent of it is in the form of oleic acid, as contrasted with 86 per cent of this substance in adult fat; the difference is made up by fats, such as palmitic acid,[40] with higher melting points. Although it does not seem feasible to assume that the Weber-Christian syndrome is merely an adult form of adiponecrosis subcutanea neonatorum, it is interesting to note that to date no chemical analysis of the subcutaneous fat has been reported in the Weber-Christian syndrome. It may be noted that infants with subcutaneous fat necrosis of the newborn are usually systemically healthy with no fever, that the disease is not thought to occur after the age of 6 months, when the chemical character of the fat in the infant becomes adult, and that the blood lipids and all the fractions are definitely increased, the iodine number being decreased[41] in this disease, reversion to normal values occurring on recovery; in addition, there are usually no residual depressed areas at the sites of the lesions.

The clinical picture strikes one as an unusually active type of lipolytic response in the subcutaneous, and possibly, in some cases, visceral, fatty tissues to some hematogenously disseminated noxa. Extensive tuberculin tests carried out by Shaffer with types of tuberculin derived from various sources demonstrated only the grade of allergic response present in most adults in the patient's locality; certainly in Shaffer's case it can be said that anergy did exist, so that a sarcoid-like reaction could be ruled out. Furthermore, in tuberculin tests car-

38. Keil, H.: Panniculitis: Its Place in Nosology, Brit. J. Dermat. **47**:512-521 (Dec.) 1935.

39. Moore, R. A.: A Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1944, pp. 694-695.

40. McIntosh, J. F.; Waugh, T. R., and Ross, S. G.: Sclerema Neonatorum (Subcutaneous Fat Necrosis), Am. J. Dis. Child. **55**:112-123 (Jan.) 1938.

41. Luzzatti, L., and Hansen, A. E.: Study of the Serum Lipids in Sclerema Neonatorum, Proc. Soc. Exper. Biol. & Med. **46**:325-329 (Feb.) 1941.

ried out on many of the other patients, some reactions were positive (which finding would rule against sarcoid) and others were negative (which observation is a point against tuberculosis). In Shaffer's case a Berkefeld filtrate of the aspirated contents of an early lesion failed to produce a reaction when injected intracutaneously or subcutaneously. Furthermore, a careful study of the sections failed to show any of the more or less characteristic features often seen in virus disease, such as balloon degeneration and inclusion bodies.[10c] It appears obvious that bacteria per se are not the cause, as is shown by the almost universally negative results in cultures of blood and in smears, cultures and inoculations of the nodular material. The 1 case, Puente's, in which staphylococci were found, as has already been mentioned, must be regarded with suspicion. Arnold[29] noted that dermatitis herpetiformis, as did his case of panniculitis, also responds to sulfapyridine more regularly than to any of the other sulfonamide compounds and that it appears to be caused by bacterial allergy. It is certainly difficult to by-pass the fact that in 10 of the 44 cases there was a fairly sound history either of development of the syndrome after the receiving of the halogens iodine and bromine or of exacerbation of the syndrome by the halogens after its establishment. In Rosenberg and Cohen's 2 cases and in Weber's second case, the onset of a relapse with appearance of fresh nodules and a spike in temperature could be produced at will by administration of a halogen and the reaction as promptly disappeared on discontinuance of the medication. The role of local or systemic foci of infection appears prominent when one consults table 1. Almost every patient had some infection or possible predisposing factor in this column, and 21 gave a picture of either dental caries or tonsillitis or both. In some instances the role of prolonged diet of one sort or another was emphasized.[42] There appears to be a gradual progressive change in the fat of the subcutaneous tissue of the skin, and possibly of the visceral fat in the severer cases, due to some unknown cause. I would suggest that the cause is an allergy of some sort, either bacterial or chemical, possibly even of virus origin, which produces the metamorphosis in the fat. This metamorphosed fat then acts as a foreign body in the tissues and calls forth a foreign body inflammatory reaction, such as is seen in pathologic study of the disease. This opinion, of course, is based only on a statistical survey and as yet is not substantiated by known fact. One is impressed with the very limited investigative work previously carried out on the panniculus adiposus, and also one is interested to note that the structure possesses definite physiologic functions and properties and that it can have certain pathologic variations.

42. (*a*) Rosenberg and Cohen.[26] (*b*) Tilden, Gotshalk and Avakian.[19]

The possibility that it may be a primary disturbance of lipid metabolism does not seem warranted in view of the almost invariably normal values for total blood lipids, cholesterol and cholesterol ester, in addition to the fact that the disease is rarely distributed over most of the body but usually affects one or a few parts alone. An interesting observation was recently made by Duran-Reynals,[32b] who compared the Weber-Christian disease in human beings with an epidemic of a fat-necrotizing disease in rabbits in 1932 to 1934 and found the diseases to be quite similar. This investigation would tend to support the theory of an infectious nature of the syndrome without, I believe, ruling out the role of allergy from the infectious agent or agents, nor would it remove the part played by halogens, the hypothesis embracing the idea that the allergy is nonspecific, resulting in Duran-Reynals' cases from some particular organism, as it apparently did in the cases in which tonsillitis or dental caries would appear to have been a predisposing factor.

In making a diagnosis of the Weber-Christian syndrome, one must first distinguish between those conditions which involve the fat lobule only secondarily and those in which the adipose tissue is primarily affected. Certain diseases may simulate the Weber-Christian syndrome clinically but be entirely different pathologically.

Nonspecific inflammatory lesions, such as cellulitis, may extend into adjacent fat, but such a picture is rarely misinterpreted. Although erythema nodosum and erythema induratum may be characterized by exudative and granulomatous inflammation of the subcutaneous adipose tissue, the fibrous septums separating the fat lobules and the connective tissue of the dermis are involved as severely as is the fat. Clearly defined angiitis is commonly seen in the various types of erythema but is not prominent in panniculitis. In cases of the true Weber-Christian syndrome, one is struck by the localization of the exudative and proliferative reaction to the fat lobule itself. The interlobular fibrous septums may be thickened, but they are relatively spared. It can be seen that the involvement of the dermis which does exist is due to inflammation of the adipose tissue about the appendages and accessory structures. Erythema nodosum is usually of shorter duration, with frequent seasonal recurrences, definite tenderness and bruiselike changes. Giant cells are rarely seen.[43] Erythema induratum usually has a protracted course, with involvement of the overlying epithelium with necrosis and ulceration. It may occasionally be found only in the subcutaneous fat. Usually, however, the degree of *Wucherungsatrophie*, the specific tubercle formation, the epithelioid cells, the

43. Pillsbury, D. M.; Sulzberger, M. B., and Livingood, C. S.: Manual of Dermatology, Philadelphia, W. B. Saunders Company, 1943, p. 13 and p. 290.

"rosette giant cells" and the pronounced vascular changes distinguish it histologically.

The subcutaneous sarcoid of Darier and Roussy may offer clinical similarties, but this condition does not usually lead to the loss of subcutaneous fat and the resultant depression on involution of the lesion, and it shows histologically such characteristics as epithelioid tubercles, pronounced fibroblastic proliferation, periarteritis and periphlebitis, which help to distinguish it from the Weber-Christian type of panniculitis. The variation in reactions, depending on the degree of anergy present, precludes too much dependence on the tuberculin test in a differential capacity. Goeckerman [44] called atention to the fact that it may be impossible to differentiate sarcoid and erythema induratum from other inflammatory processes in the early stages.

Dermatomyositis involves muscle as well as skin, and there is severe pain on movement and considerable muscular weakness.

Nodular syphilis and leprosy can be ruled out by serologic tests and biopsy smear. Dermal manifestations of the types of lymphoblastoma [45] can be diagnosed by biopsy and by attention to the systemic aspects of the disease.

In adiposis dolorosa, the nodules remain unchanged for years and are painful. The nodules are encapsulated and composed of large numbers of small, oval, fatty bodies, connected with each other and with the capsule by delicate fibrous bands. The capsule is composed of several layers of well developed connective tissue. This tissue is highly vascular, and between the vessels is a reticular tissue, denser in some areas than in others and enclosing a large number of mononuclear cells, a few polymorphonuclear cells and a large number of cells staining a tawny color by the Van Gieson method. Scattered through the granular, tawny masses, many of the mononuclear type of cells occur. In other areas granules of blood pigment are present.

Rare types of thrombophlebitis [46] may show the clinical picture of relapsing febrile nodular panniculitis, but evidence of venous inflammation and thrombus formation is found in the histologic examination.

Agglutination tests may be used to clarify suspicion of brucellosis, typhoid or paratyphoid that may be aroused by the relapsing type of fever associated with Weber-Christian disease.

The lesions of morphea (circumscribed scleroderma) are plaquelike, slow to develop and regress and leave the skin shriveled and bound to the underlying tissues.

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44. Goeckerman, W. H.: Sarcoids and Related Lesions: A Report of Seventeen Cases; Review of the Recent Literature, Arch. Dermat. & Syph. **18**:237-262 (Aug.) 1928.

45. Reimann, H. A.: Havens, W. P., and Herbert, P. A., cited by Friedman.[2b]

46. Barker, N. W., cited by Bailey.[2a]

Similar pathologic pictures with dissimilar clinical features can be produced by various agents. Localized atrophy and tumefaction of subcutaneous fat have occurred in persons after injection of insulin, camphor, oil and other agents.[47]

Subcutaneous fat necrosis of the newborn has already been discussed.[48]

Diffuse atrophy of subcutaneous fat without evidence of previous inflammatory changes (lipodystrophy) as a rule offers no difficulty in the differential diagnosis. In this condition there is complete removal of the subcutaneous fat from the affected areas.[49] The face and neck are usually affected, but Bigler has reported a case in which the loss of fat was on the legs.[50]

Primary involvement of the fat lobule occurs in traumatic fat necrosis, which may closely simulate the Weber-Christian syndrome. Indeed, many cases previously diagnosed as traumatic fat necrosis, particularly of the breast, without the history of trauma, may possibly have been examples of the Weber-Christian syndrome of mild localized degree; and the concomitant nodules on other parts of the body, such as the legs, may have passed unnoticed. Binkley[10a] stated the belief that the syndrome should be considered in any case of possible traumatic fat necrosis or carcinoma of the breast.

The types of lipogranuloma described by the Russian pathologist Abrikossoff[51] should be mentioned. The nodules were observed in obese persons during the period of convalescence from infectious diseases, especially relapsng fevers and typhus. The lesions made their appearance predominantly in the panniculus adiposus but also in the retroperitoneal adipose tissue, the omentum and the mesentery. Although the original papers were not available to me it appears from the summaries by Abrikossoff that the Russian authors were referring to a pathologic process in many respects similar to that seen in the Weber-Christian syndrome.

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47. (*a*) Rowe and Garrison.[32f] (*b*) Sundwall, J.: Localized Areas of Atrophy of Fat Cells in Derma and Subcutaneous Tissue, J. Cutan. Dis. **36**:145 (March) 1918.

48. (*a*) Shong, G., and Cowan, A.: Subcutaneous Fat Necrosis of New-Born, Ohio State M. J. **31**:34-35 (Jan.) 1935. (*b*) Tow, A.: Scleroderma (Adiponecrosis Subcutanea Neonatorum) in Diseases of the New-Born, New York, Oxford University Press, 1937, p. 436.

49. Parmellee, A. H.: Lipodystrophy, in Brenneman, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 1, chap. 41, pp. 1-7.

50. Bigler, J. A.: Loss of Subcutaneous Fat of the Lower Extremities (Lipodystrophy), J. A. M. A. **112**:627-628 (Feb. 18) 1939.

51. (*a*) Abrikossoff, A., cited by Friedman.[2b] (*b*) Abrikossoff, A., cited by Ungar.[2d]

Treatment of the syndrome has been to a large extent unsatisfactory. The condition has been regarded as chronic, relapsing and self limited, with a tendency eventually to burn itself out. Such an attitude should be regarded with suspicion, as it has already been shown that neither is the disease as innocuous as has been assumed, nor does it disappear so readily. In the past, removal of foci of infection, discontinuance of the use of halogens, a diet high in vitamins, roentgen therapy, ultraviolet irradiation and sulfonamide therapy have all been tried, with varying success. Successful treatment of 1 case was reported by Arnold, who used sulfapyridine. Recently, Zee obtained an apparent cure with the use of penicillin. It would appear, at present, that general systemic measures, local massage and heat and a trial of the sulfonamide drugs, in adequate dosage, or penicillin give the best outlook in the treatment. Miller and Kritzler [2c] expressed the opinion that the sulfonamide compounds were useless in the treatment, but from a careful analysis of their article it would appear that, the sulfonamides at the time of their writing having been in the early days of clinical trial, these authors used inadequate doses and obtained insufficient blood levels to secure the maximum therapeutic efficacy with all the three drugs (sulfanilamide, sulfathiazole and sulfadiazine) which they employed, with the possible exception of sulfathiazole.[52] It may also be noted that their patient showed early satisfactory temporary improvement with small doses of sulfanilamide, treatment with which was then discontinued, possibly because of the general improvement. There was an immediate exacerbation of symptoms, but afterward the patient was refractory to all of the sulfonamide drugs given.

COMMENT

Although the etiology is unknown, the clinical-pathologic features suggest that panniculitis of the Weber-Christian type is a syndrome rather than a disease entity. It would appear that it is the result of some noxious stimulus producing a metamorphosis in the subcutaneous fat, and possibly also in the visceral fat in the severer cases, the fat acting as a foreign body and calling forth a foreign body response, with the reticuloendothelial system playing a large part in the syndrome. It is

52. (*a*) Goodman, L., and Gilman, A.: The Pharmocological Basis of Therapeutics, New York, The Macmillan Company, 1941, pp. 1021-1103. (*b*) Useful Drugs, Council on Pharmacy and Chemistry, American Medical Association, edited by K. A. Hatcher, ed. 12, Chicago, American Medical Association, 1941, p. 205. (*c*) Kolmer, J. A., and Tuft, L.: Clinical Immunology, Biotherapy, and Chemotherapy in the Diagnosis, Prevention, and Therapy of Disease, Philadelphia, W. B. Saunders Company, 1941, pp. 297-298. (*d*) The Merck Manual of Therapeutics and Materia Medica, ed. 7, Rahway, N. J., Merck & Co., Inc., 1944, pp. 986 and 1336. (*e*) Warkentin, J., and Lange, J.: Physician's Handbook, ed. 2, Chicago, Medical Publishers, 1942, p. 239.

suggested that the mechanism may be in the form of a nonspecific type of allergy. The liquefaction and pus occasionally occurring in the nodules probably indicate merely a severer phase of the more commonly seen nonsuppurative reaction. A somewhat different view was propounded by Ungar,[2d] who stated the belief that nonsuppurative changes are due to tissue injury by fatty substances liberated in the course of destruction of fat cells by suppurative inflammation. In either instance, however, it would appear that the nonsuppurative changes have no specific significance in the pathologic process of the Weber-Christian syndrome.

SUMMARY

1. The syndrome relapsing febrile nodular panniculitis, or Weber-Christian disease, is discussed and the forty-fourth case reported.

2. The literature is reviewed, and the pertinent points are summarized in two tables.

3. The pathology and etiology are discussed, and the suggestion is advanced that the etiology may be on the basis of a nonspecific tissue allergy.

4. The differential diagnosis and treatment are presented.

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ENHANCING PHOTODYNAMIC EFFECT OF SOLUTIONS OF CRUDE COAL TAR ON THE SKIN

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THE WORK reported in this paper is part of a problem concerned with the development of a method for the effective treatment of psoriasis by photodynamic action.

Lewin [1] was the first to recognize that coal tar products are capable of rendering the skin sensitive to sunlight. He found that most of a large group of persons who came repeatedly into contact with certain coal tar products had dermatitis and itching when they were exposed to sunlight. Other investigators in this field included Herxheimer and Nathan,[2] Fleishhauer,[3] Doniach and Mottram [4] and Foerster and Schwartz.[5] These early workers established the fact that the action spectrum for tar lies between 3,300 and 5,000 angstrom units and that it is not possible to credit the photosensitizing action of coal tar residues very definitely to any one group of compounds.[6] An attempt to employ photodynamic action therapeutically in dermatology was made by Goeckerman [7] when he applied 5 per cent crude coal tar in an ointment of zinc oxide and petrolatum to lesions of psoriasis and irradiated the area with a mercury vapor lamp. He and also subsequent workers employed this procedure, unmodified and modified, and believed

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1. Lewin, L.: Ueber photodynamische Wirkungen von Ihaltsstoffen des Steinkohlenteerpechs am Menschen, München. med. Wchnschr. **60**:1529, 1913.

2. Herxheimer, K., and Nathan, E.: Ueber Sensibilisierung der Haut durch Carboneol gegenüber Sonnenlicht und eine dadurch bedingte Dermatitis solaris, Dermat. Ztschr. **24**:385, 1917.

3. Fleischhauer, L.: Ueber die sensibilisierende Wirkung des Teerpräparates Liantral, Strahlentherapie **36**:144, 1930.

4. Doniach, I., and Mottram, J. C.: Sensitization of the Skin of Mice to Light by Carcinogenic Agents, Nature, London **140**:588, 1937.

5. Foerster, H. R., and Schwartz, L.: Industrial Dermatitis and Melanosis Due to Photosensitization, Arch. Dermat. & Syph. **39**:55 (Jan.) 1939.

6. Blum, H. F.: Photodynamic Action and Diseases Caused by Light, American Chemical Society Monograph Series, no. 85, New York, Reinhold Publishing Corporation 1941, p. 265.

7. Goeckerman, W. H.: Treatment of Psoriasis, Northwest Med. **24**:229, 1925.

it to be the most satisfactory method yet devised for the treatment of psoriasis, which, however, it did not cure.

I felt that a certain technic was necessary if photodynamic action were to be achieved by the procedure and that this action could be enhanced by further modification of the solutions of crude coal tar employed. This paper presents the results of the studies of these problems.

METHODS AND RESULTS

The current method of attempting to produce a photodynamic response in the skin with tar consists in painting an area with solution of coal tar N. F. (a 20 per cent solution of coal tar in alcohol, with quillaja) and irradiating the area with a mercury vapor arc lamp as soon as the applied solution has dried. The following experiment shows that this procedure does not produce any photochemical reaction on the treated skin.

Solution of coal tar N. F. and 5 per cent solutions of crude coal tar in acetone, alcohol, carbon tetrachloride, chloroform and ether, respectively, were each painted on corresponding sites on both forearms and the dorsa of 6 subjects. The solutions were permitted to dry, and immediately afterward the right side was exposed to an erythema dose of ultraviolet radiation from a mercury vapor lamp, while the left side was covered. Following this treatment, the left side was exposed to an erythema dose of ultraviolet radiation from a carbon arc lamp using a sunshine® carbon electrode, with the right side covered. Then the same solutions were applied on fresh sites, on the forearms and the dorsa of 6 subjects. In this second experiment the applications were made daily for three consecutive days, and immediately after the last application the subjects were exposed to erythema doses of light from both the mercury vapor and the carbon arc lamps, as on the earlier occasion.

In each case the areas to which the various tar solutions had been applied showed no effect from the exposure to light, whereas the surrounding zones displayed a bright erythematous reaction.

The failure of the tar solutions to produce photosensitization in this instance was due to the fact that the surface film of tar acted as a screen or filter which prevented the radiation of specific wavelength from reaching the skin.

To demonstrate that crude coal tar solutions can produce photosensitization, the following experiments were done:

The six solutions used in the former experiment were applied to the sides of both forearms and the dorsa of 6 subjects for three consecutive days. On the fourth day the areas were washed thoroughly with soap and water and afterward with alcohol. This washing removed only the surface film of tar, as under the Wood light the areas which had been painted and then washed still fluoresced brightly. The right side was then exposed to an erythema dose of ultraviolet radiation from a mercury vapor lamp, with the left side covered, and, next, the left side was exposed to an erythema dose of light from a carbon arc lamp using a sunshine® carbon, with the right side covered.

The results with the mercury vapor lamp were as follows: Erythema of equal intensity appeared on both the painted and the unpainted areas but was more rapid in its development in the former. The only materials which produced a well demarcated reaction on the painted skin, in 2 of the 6 subjects studied, were solution of coal tar N. F. and the solution in carbon tetrachloride. With the carbon arc lamp the photodynamic reaction was greater in intensity than with the mercury vapor arc lamp and was provoked by all the tar solutions except the alcoholic. The most effective solvents for the tar, as was manifested by the intensity of reaction following irradiation with the carbon arc lamp, were, first, carbon tetrachloride and, second, acetone.

Having established the fact that tar solutions can be used to produce photosensitization, I then made an attempt to produce a solution which would be a more effective photosensitizer than any previously used. The properties desired for this solution were, first, the ability to penetrate the skin and thus, probably, to come into more intimate contact with the reacting tissue and, second, capability of ready removal from the surface of the skin by washing. It was felt that the addition of a wetting agent would accomplish both of these conditions.

To demonstrate a more effective tar solution for photosensitization I performed the following experiment, in which carbon tetrachloride was selected as the solvent for the tar on the basis of the foregoing work:

Five grams of crude coal tar was added to 60 cc. of carbon tetrachloride, 30 cc. of acetone, 5.5 cc. of propylene glycol and 4.5 Gm. of aerosol O T® (the dioctyl ester of sodium sulfosuccinate in 99 to 100 per cent concentration). The mixture was then filtered. The filtrate, as well as solution of coal tar N. F. and a 5 per cent solution of crude coal tar in carbon tetrachloride, was painted on the abdomen of 6 subjects on three successive days. On the fourth day the areas were washed thoroughly with soap and water followed by alcohol and were then exposed to an erythema dose of light from a carbon arc lamp using a sunshine® carbon.

All three areas to which the tar had been applied showed an erythema which appeared earlier than did that on the surrounding untreated skin. Twelve hours after irradiation the erythema of the painted sites was more intense than was that of the surrounding skin, and, after the third day, pigmentation was present in all three sites. The coal tar solution containing the wetting agent produced the most intense reaction. Next in intensity was the reaction caused by the solution in carbon tetrachloride, and least was that from the solution of coal tar N. F.

COMMENTS

Foerster and Schwartz [5] demonstrated the photosensitizing effects of pitch, containing a high percentage of crude coal tar, when sunlight was the source of radiant energy. They were unable to obtain any

reaction with the mercury vapor lamp or the carbon arc lamp using a therapeutic C carbon electrode. The work presented in this paper does not necessarily conflict with the results of Foerster and Schwartz for the reason that the carbon arc radiation was not produced in identical fashion in both series of experiments. The quality of radiation from the carbon arc depends on the following factors[8]: the size and the kind of electrodes, the direction of the current, when direct current is used through combinations of neutral-cored and impregnated carbons, and the amount of the electric current. The limits of the effective spectrum for photodynamic action allow only the use of the sun and of the carbon arc for the production of photosensitization of the skin with tars. To increase the intensity of photodynamic action on the skin beyond that reported in this paper, it will be necessary for one to take into account the factors affecting carbon arc radiation, the nature of the photosensitizing chemical and the solvent as well as the wetting agent employed in conjunction with this chemical.

SUMMARY

The inclusion of a wetting agent in solutions of crude coal tar, in conjunction with the use of the carbon arc as a source of radiation, enhances the photodynamic action of such solutions on the skin.

8. Coblentz, W. W.: Sources of Ultraviolet and Infra-Red Radiation Used in Therapy: Physical Characteristics, J. A. M. A. **132**:378 (Oct. 19) 1946.

SUPERNUMERARY EARS

Report of Three Cases

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ANOMALIES of the branchial clefts and arches are among the commoner congenital aberrations. Greater interest in these cases manifested itself in the last half of the nineteenth century, at which time many reports were added to the literature. In England, Birkett,[1] Bland Sutton[2] and others[3] and in Germany, Ferdinand Schmitz[4] and Virchow[5] added materially to the subject with illustrative case reports and studies. Observers in other countries have from time to time enriched the knowledge of this subject by studying and reporting cases which have come to their attention. One of the most comprehensive reports was contributed by Carp and Stout[6] in 1928. These authors classified a series of 32 cases according to embryologic development.

There has been a difference of opinion as to the nomenclature used. By supernumerary appendages we mean the lesions occurring on the face and neck. Those occurring on the face are called supernumerary auricles (or ears), and those on the neck, cervical auricles.

Polyotia is a term frequently applied to the supernumerary auricles about the auditory meatus or in its proximate vicinity. It is interpreted to mean more than one ear on either or both sides of the head. This use is technically incorrect because the complete ear apparatus is never duplicated.

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1. Birkett, J.: Congenital Supernumerary and Imperfectly Developed Auricles on the Sides of the Neck, Tr. Path. Soc. London **9**:448, 1857-1858.

2. Sutton, J. B.: Supernumerary Auricles, Illust. M. News **1**:320, 1888.

3. Clarke, W. B.: Supernumerary Auricles, Illust. M. News. **1**:321, 1888. Lake, R.: Double Supernumerary Auricle, ibid. **1**:322, 1888.

4. Schmitz, F.: Ueber Fistula auris congenita und andere Missbildungen des Ohres, Halle, Lipke, 1873.

5. Virchow, A.: Ein neuer Fall von Halskiemenfistel, Arch. f. path. Anat. **32**:518, 1865.

6. Carp, L., and Stout, A. P.: Branchial Anomalies and Neoplasms, Ann. Surg. **87**:186, 1928.

Supernumerary appendages have also been called nevus cartilaginous [7] because they most frequently contain cartilage. This cartilage is a necessary part of the condition, as it proves derivation from the branchial apparatus. There are three usual locations for accessory auricular appendages: (1) on the tragus or in its proximate vicinity, (2) along a line drawn from the tragus to the angle of the mouth, and (3) on the sides of the neck along the sternocleidomastoid muscle.

Supernumerary appendages are most commonly found on the tragus or in its immediate vicinity. In the other two locations, they may be seen, though rarely.

The external ear consists of the auricle, or pinna, and the external acoustic meatus. Histologically the auricle consists of a thin plate of yellow elastic cartilage covered by skin anteriorly and by skin and some subcutaneous tissue posteriorly. The ear develops about the first branchial cleft. Three tubercles develop above the mandibular arch to form the tragus, the crus of the helix and the helix; three form from the hyoid arch to form the antihelix, the lobule and the antitragus. Undoubtedly in many cases the auricular appendages are anomalies of these tubercles rather than of the branchial arch itself.

Cervical auricles originate from the other branchial clefts, sometimes in association with branchial fistulas. They are seen along the anterior border of the sternocleidomastoid muscle at the level of the hyoid cartilage or just above the sternoclavicular articulation.

The lesions may assume many different shapes and forms. Some are elevated tabs or nodules; some are small, dimple-like lesions with central teats. Not in all lesions can the underlying cartilaginous plaque be palpated. It is also observed that frequently these anomalies are associated with other congenital malformations. It is further observed that such anomalies may appear in more than one generation of the same family—in case 2 reported here, supernumerary ears had appeared in three generations of one family.

The common error made in diagnosing these cases clinically is considering the lesions to be fibromas. Histologic examination of the lesion will show its true nature, since cartilage is always found high in the subcutis or in the cutis. The presence of cartilage is an outstanding feature of the condition, because cartilage normally is not seen in this location. The accompanying figures illustrate the presence and location of cartilage.

7. Aoki, in Jadassohn, J., and Zieler, K.: Ikonographia dermatologica, Berlin, Urban & Schwarzenberg, 1937, no. 41, p. 256.

Costello and Shepard [8] in 1939 reported on the literature and added reports of 4 additional cases. Three photographs were shown in which the lesions were on the tragus or in the cheek near the tragus. We wish to report 3 cases: 2 in which the supernumerary ears were along

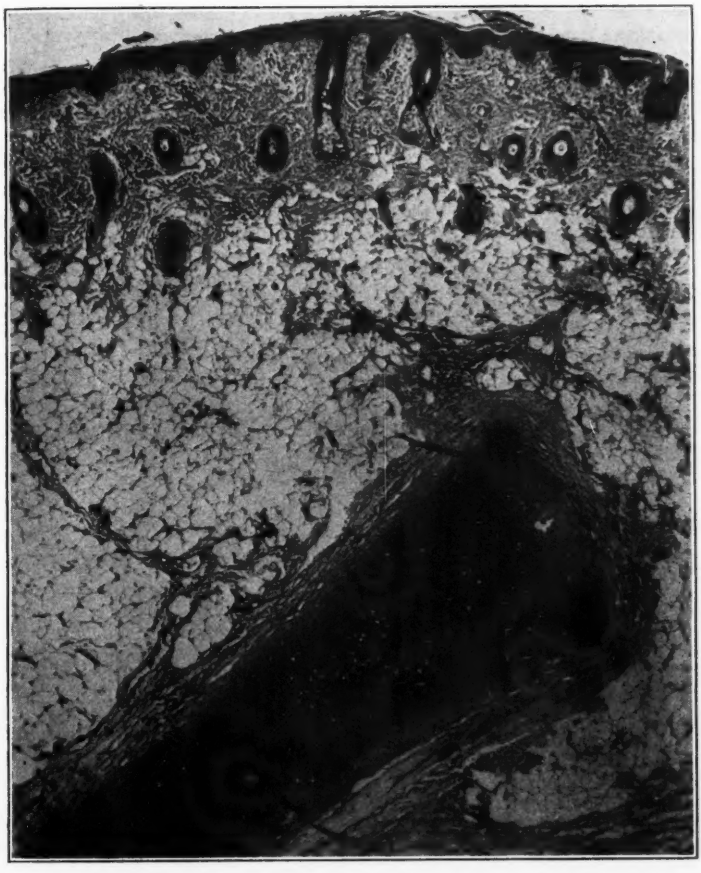

Fig. 1.—Showing within the subcutis a large oval mass of cartilaginous tissue surrounded by a fibrous capsule.

the line from the tragus to the angle of the mouth, and a third in which a cervical auricle was found near the sternoclavicular junction.

8. Costello, M. J., and Shepard, J.: Supernumerary External Ears, Arch. Otolaryng. **29**:695 (April) 1939.

REPORT OF CASES

CASE 1.—S. J., an 8 month old female infant, was first seen on March 4, 1942. The mother stated that she noticed a defect in the middle of the baby's right cheek at the time of birth. This defect had not changed in size, shape or color during the eight months.

Examination revealed a circular, chamois-hued, macular patch about 1 cm. in diameter just midway between the angle of the mouth and the tragus. Palpation showed it to be of the same consistency as the normal skin.

A clinical diagnosis of nevus—possibly a soft fibroma—was made. Surgical removal was advised. On April 25 the entire lesion was removed with the use of procaine hydrochloride (novocaine hydrochloride®) anesthesia and submitted as a biopsy specimen.

The histologic study (see fig. 1) was made by Dr. David Satenstein and Dr. Wilbur Sachs. The microscopic report was "development of cartilage tissue." The description was as follows: "Within the subcutaneous tissue was a large, oval mass of cartilage, which was surrounded by a fibrous capsule. Besides this observation (cartilage where one would not expect to find it) the slide showed nothing abnormal."

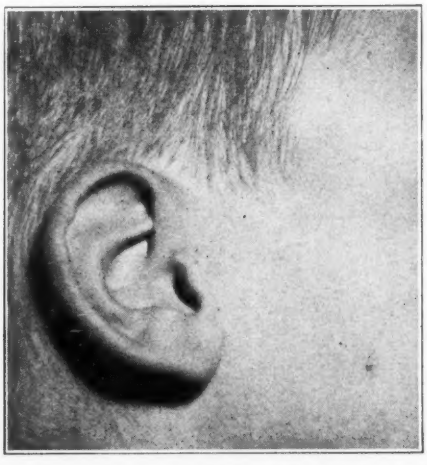

Fig. 2 (case 2).—G. K., aged 21 months, showing a chamois-colored patch 1 cm. in diameter, with a central elevation, on the right cheek. The patch had been present since birth.

When we discussed the slide with Dr. Satenstein he suggested the possibility that the lesion was a supernumerary ear.

CASE 2.—G. K. (fig. 2) a male baby aged 21 months was first seen by us on Sept. 14, 1944. The mother stated that the baby had been born with a small mass on the right cheek and that he persistently picked and irritated it. Examination revealed a chamois-hued patch about 1 cm. in diameter, with a central elevation. Palpation showed it to be of the same consistency as the normal skin. The diagnosis of supernumerary ear was made. The mother then stated that

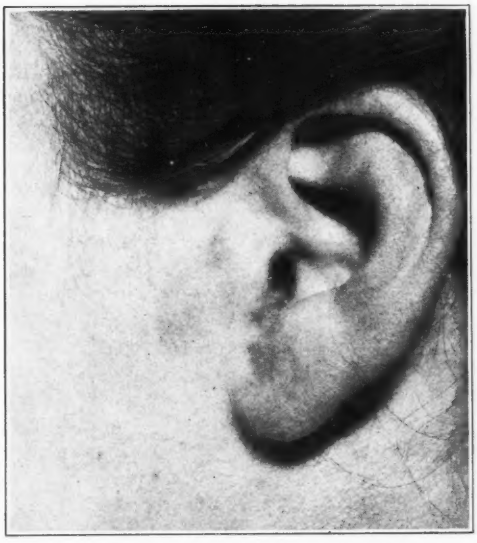

Fig. 3.—Mother (case 2), aged 28, with remains of a treated elevation in front of the left tragus.

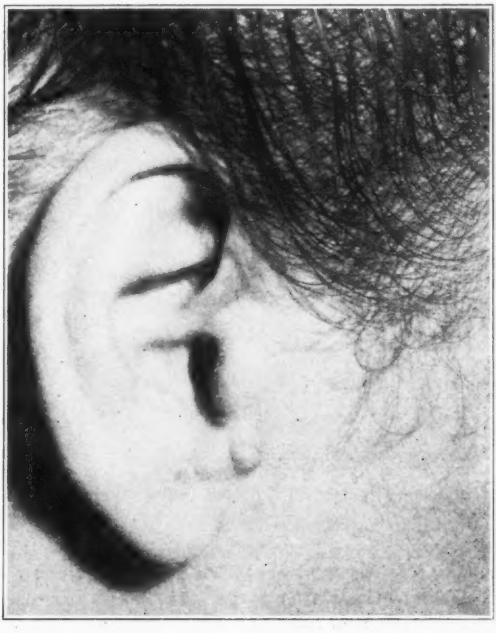

Fig. 4.—Grandmother (case 2), aged 49, with a supernumerary ear evident below the right tragus.

she had had similar lesions on both sides of her head (fig. 3) and that they had been treated by "tying off" when she had been a child. Examination of the mother showed somewhat elevated scars in front of both tragi. Questioning further revealed that the maternal grandmother (fig. 4) had borne a similar lesion on the right side of her head since birth.

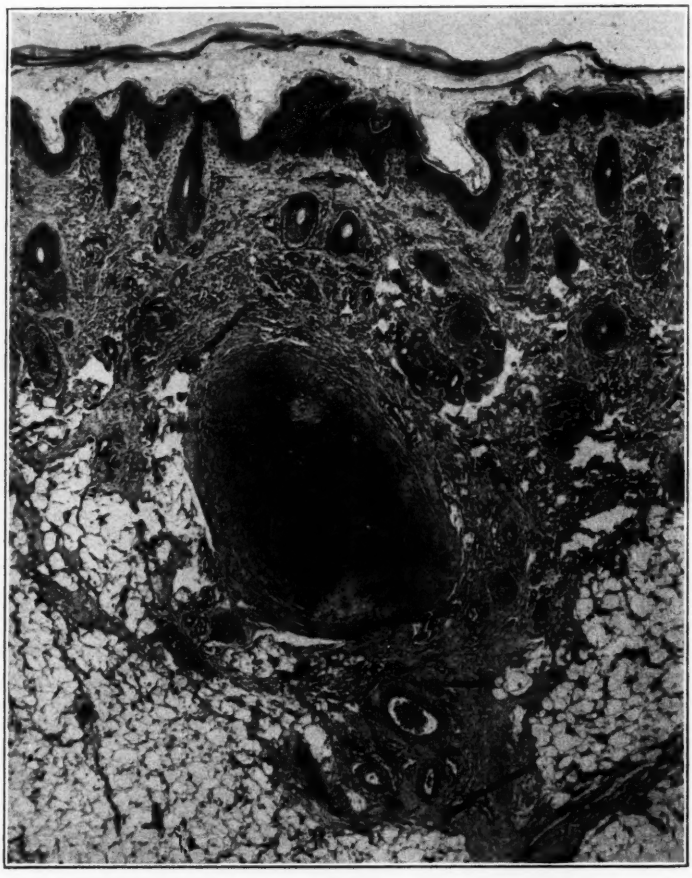

Fig. 5.—Cartilaginous tissue with a fibrous capsule high up in subcutis (G. K., case 2).

The entire lesion was removed from the child with the use of procaine hydrochloride anesthesia and submitted for biopsy. The microscopic diagnosis by Dr. Wilbur Sachs was "supernumerary ear" (fig. 5). The histologic description was as follows:

"In the center of the section, extending from the midcutis to fat, was an oval cartilaginous mass. About this was a circumscribed increase in the fibrous tissue, within which there was a diffuse fibroblastic cell infiltration. The vessels of the midcutis and the upper cutis were moderately dilated, and there was a considerable cellular infiltration, partly focal and partly diffuse. The cells were composed chiefly of small round cells, wandering connective tissue cell and plasma cells. The overlying epidermis showed no important change. There were numerous hair follicles which appeared immature and not fully developed. There appeared to be only a small amount of cutis present in relation to the amount of subcutis.

"Diagnosis: The microscopic picture was concomitant with the features found in cases of supernumerary ear. Some irritation was present."

Fig. 6.—Cervical auricle near the left sternoclavicular articulation (case 3).

CASE 3.—S. A. (fig. 6), aged 5, was seen on May 1, 1945, for herpes simplex on the right cheek. Routine examination revealed a small mass near the left sternoclavicular junction. Permission was not granted for its removal. The clinical diagnosis was cervical auricle.

COMMENT

S. J., now 6 years old, has been examined at regular intervals. She was last seen on Oct. 10, 1945. There is a fine, soft scar at the site of the previous lesion. No other sequelae have resulted from removal of the lesion.

As far as we can ascertain, no tumor mass or malignant changes have developed from these supernumerary ears. According to the observations by Carp and Stout,[9] in cases in which malignant neoplasms have developed they have been in association with branchial fistulas.

9. Carp and Stout,[6] p. 194.

SUMMARY

Two cases of supernumerary ears along a line drawn from the anterior tragus to the angle of the mouth are reported. In the first, diagnosis was made only after the histologic examination revealed the features of a supernumerary ear. The second, also a case of a flat lesion but one with a central elevation, was diagnosed clinically. Diagnosis was verified on histologic examination.

In the third case there was a cervical auricle, and the diagnosis was made clinically.

37-38 One Hundred and Fourth Street.

LIPOMELANOTIC RETICULOSIS OF LYMPH NODES IN A CASE OF LICHEN PLANUS

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AND
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LOS ANGELES

IN 1891 Jadassohn [1] described some peculiar histopathologic changes in the lymph nodes observed in a case of pityriasis rubra (Hebra). Subsequently, Pautrier and Woringer [2] made a preliminary report on this condition, which they termed "lipomelanotic reticulosis"; and in 1937 they published a detailed study [3] of this disorder, which has been observed in conjunction with a variety of dermatoses. This entity can best be described as lymphadenopathy characterized by proliferation of reticular cells, phagocytosis of fat and melanin and pleomorphic cellular infiltrations.

In 1941 Soloff [4] reported the occurrence of this specific alteration of lymph nodes in a case of acute miliary tuberculosis. However, in this case it was clearly established that the lipomelanotic changes were not associated with the tuberculosis but had arisen consequent to an intensely pruritic, chronic-recurrent, occupational dermatosis of the groins. Subsequent reports have emphasized the association of lipomelanotic reticulosis with some types of lymphoblastoma, as well as with a variety of diverse pruritic dermatoses, such as arsenical exfoliative dermatitis, chronic lichenified eczema, prurigo, seborrheic derma-

From the Department of Dermatology and Syphilology, University of Southern California School of Medicine.

1. Jadassohn, J.: Ueber die Pityriasis rubra (Hebra) und ihre Beziehungen zur Tuberculose (nebst Bemerkungen über Pigmentverschleppung aus der Haut), Arch. f. Dermat. u. Syph. **23**:941-979, 1891.

2. Pautrier, L. M., and Woringer, F.: Note préliminaire sur un tableau histologique particulier de lésions ganglionnaires accompagnant des éruptions dermatologiques généralisées, prurigineuses, de types cliniques différents, Bull. Soc. franç. de dermat. et syph. **39**:947-955, 1932.

3. Pautrier, L. M., and Woringer, F.: Contribution à l'étude de l'histophysiologic cutanée: À propos d'un aspect histo-pathologique nouveau du ganglion lymphatique; La réticulose lipo-melanique accompagnant certaines dermatoses généralisées; Les échanges entre la peau et le ganglion, Ann. de dermat. et syph. **8**:256-273, 1937.

4. Soloff, L. A.: Lipomelanotic Reticular Hyperplasia of Lymph Nodes: Report of a Case, J. Lab. & Clin. Med. **27**:343-346, 1941.

titis, stasis dermatitis and exudative chronic discoid and lichenoid dermatosis (Sulzberger and Garbe).[5]

The patient who is the subject of this report had, on clinical examination, the characteristic manifestations of lichen planus and, in addition, moderate enlargement of several lymph nodes. Microscopic examination revealed the features of lichen planus and the typical picture of lipomelanotic reticulosis. So far as we know, this is the first report of lipomelanotic reticulosis in association with lichen planus.

REPORT OF CASE

L. H., a 70 year old woman, was first seen by us in December 1946, when she complained of an itching eruption of one month's duration. The dermatosis,

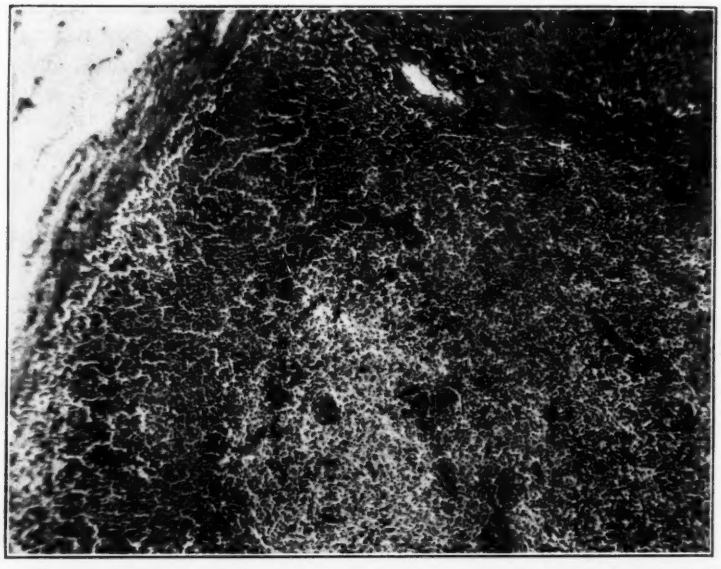

Fig. 1.—Granulomatous hyperplasia of lymph node in lipomelanotic reticulosis (× 22).

which had begun on her hands, spread gradually to the extremities and trunk; pruritus meanwhile increased in intensity.

Physical examination disclosed features normal for a woman of the patient's age. Scattered over the extremities were large and small, discrete and confluent plaques composed of the erythematous, polygonal, flat-topped papules characteristic of acute, generalized lichen planus. The mucous membranes were not involved. The enlarged lymph nodes in the axillas and in the groins were moderately firm but not tender. Examinations of the blood, performed at intervals, disclosed no abnormalities.

5. Kocsard, E.: Three Cases of Exudative Chronic Discoid and Lichenoid Dermatosis (Sulzberger and Garbe) (in Shanghai), J. Invest. Dermat. **10**:1-9, 1948.

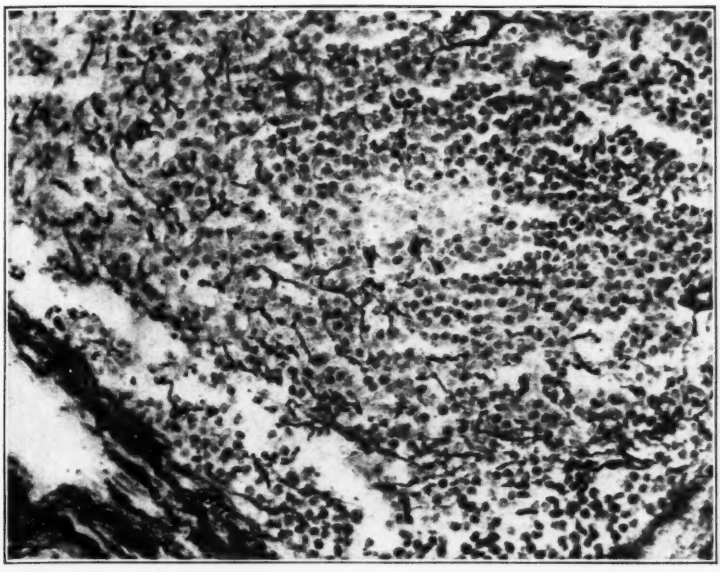

Fig. 2.—Reticular pattern of hyperplastic lymph node in lipomelanotic reticulosis (reticulum stain; × 38.6).

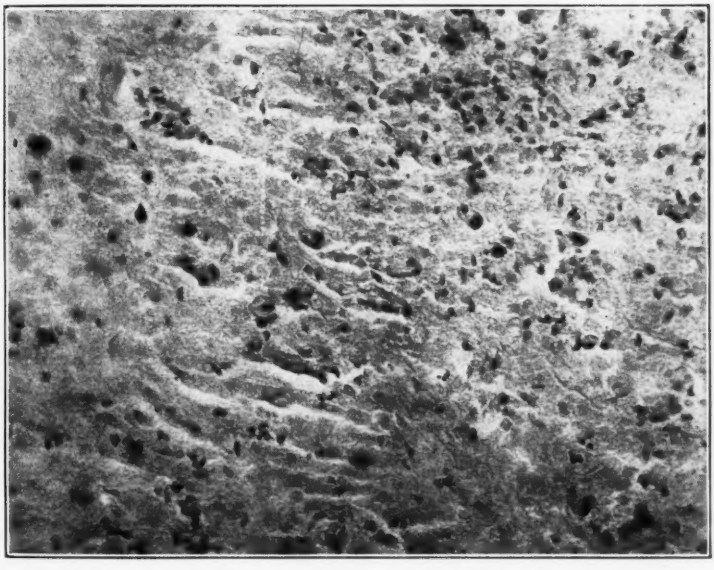

Fig. 3.—Chromatophores in lipomelanotic reticulosis (silver stain; × 220).

Biopsy of a cutaneous specimen revealed features typical of lichen planus. Microscopic study of a large node from the right groin (removed elsewhere [6]) showed that the architecture had been obscured by a proliferation of large reticuloendothelial cells, most evident in the cortex but also present in some portions of the medulla. In the cytoplasm of the poorly outlined cells were vacuoles which gave a positive reaction to stains for fat. Special stains indicated that the brown pigment irregularly clumped in phagocytic cells was melanin and not hemosiderin. Small numbers of plasma cells, eosinophils and polymorphonuclear leukocytes were scattered throughout the excessively vascularized node.

There were several severe exacerbations, but over a period of six months the eruption, as well as the enlargement of the lymph nodes, gradually subsided.

COMMENT

Consideration of the features of our case and of those previously reported appears to show that in all instances the dermatoses which preceded the changes in the lymph nodes, though etiologically and morphologically widely divergent, were usually generalized, chronic or chronic-recurrent and intensely pruritic. The lymphadenopathy was sometimes widespread but was usually most pronounced in the inguinal and the axillary areas. Affected lymph nodes were somewhat firm, discrete and not tender. Grossly, the cortex appeared clearer than normal, and the melanin stood out as scattered brown specks.

The hyperplasia of reticular cells is assumed to result from their continued efforts to phagocytose large quantities of melanin and lipid material, presumably cholesterol. The amount of sudanotropic material is greater [7] in nodes exhibiting lipomelanotic reticulosis than in those with most other lesions. In normal lymph nodes or in those undergoing follicular or reticular hyperplasia, melanin and fat are either absent or present only in small amounts.

Normally, most of the melanin formed by melanoblasts in the basal cell layer of the epidermis is eliminated in the process of keratinization, although minute amounts may be carried away by the regional lymphatics. The trauma of continued scratching may result in the production of abnormal quantities of melanin, most of which pigment is transferred to the dermis. Scratching may even mechanically propel pigment into dilated regional lymphatics and thence into the lymph nodes. A comparable mechanism is postulated to account for the transfer of lipid material to the nodes.

The amounts of lipid and melanin in the abnormal lymph nodes appear to be directly proportional to the severity and duration of the pruritus. Although chronic pruritic inflammation seems to be the

6. Dr. E. M. Butt, who removed the lymph node, placed the sections at our disposal.

7. Laipply, T. C.: Lipomelanotic Hyperplasia of Lymph Nodes: Report of Six Cases, Arch. Int. Med. **81**:19-36 (Jan.) 1948.

primary causative factor and the proliferative changes in the lymph nodes secondary, it is not clear why this peculiar hyperplasia occurs in only a small proportion of cases of the various dermatoses in which it has been observed.

The frequent occurrence of lipomelanotic reticulosis in patients with cutaneous lymphoblastoma or a precursor of it has sometimes led to the erroneous assumption that the changes in the lymph nodes are part of the malignant process; in fact, the pattern may simulate that of Hodgkin's disease to a remarkable degree. However, it has been proved beyond doubt [8] that the lipomelanotic process is only a concomitant of the lymphomatous lesion. Nodes may exhibit a lymphoblastic process and lipomelanotic changes at the same time.

SUMMARY

The occurrence of lipomelanotic reticulosis of lymph nodes in a case of lichen planus is reported. This peculiar lymphadenopathy is associated with chronic pruritus and scratching. No adequate explanation has been advanced for its occurrence in only a small proportion of the instances of the various dermatoses with which it is known to be associated.

3875 Wilshire Boulevard (5).

8. Laipply,[7] Montgomery, H., and Watkins, C. H.: Monocytic Leukemia: Cutaneous Manifestations of the Naegeli and Schilling Types; Hemocytologic Differentation, Arch. Int. Med. **60**:51-63 (July) 1937.

TREATMENT OF LUPUS VULGARIS WITH CALCIFEROL (VITAMIN D_2)

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THE TREATMENT of cutaneous tuberculosis with calciferol (vitamin D_2) had its beginnings and development in Europe. It is not the purpose of this paper to survey the European literature since there is an American report on this (Michelson and Steves [1]). The incidence of cutaneous tuberculosis is so much greater in Europe than in the United States that large series of cases are difficult to accumulate in this country. Since the authors have had the opportunity to follow 3 cases of lupus vulgaris after treatment with calciferol it was felt that a report of their findings is justified to add to the American experience with this treatment.

Calciferol is prepared by exposure of ergosterol to ultraviolet irradiation. The doses of calciferol used in the treatment of cutaneous tuberculosis are large compared with the usual maintenance doses. Indeed, the best therapeutic results are obtained at or near the dose which may produce toxic symptoms (Macrae [2] and Dowling and Thomas [3]). As yet the exact schedule of treatment has not been standardized. A brief summary of the suggested schedules of treatment might be helpful.

Feeny [4] suggested a dose of 100,000 units daily, to be raised to 150,000 units if the patient indicated tolerance or was not progressing satisfactorily. He reported that this treatment was more beneficial than any other form of treatment used by him.

The experience of Macrae [2] is interesting and significant. He treated 20 patients in whom the infections were so far advanced that

1. Michelson, H. E., and Steves, R. J.: Treatment of Cutaneous Tuberculosis with Large Doses of Vitamin D_2, Arch. Dermat. & Syph. **56**:317 (Sept.) 1947.

2. Macrae, D. E.: The Use of Calciferol in Tuberculous Conditions, Lancet **1**:135 (Jan. 25) 1947.

3. Dowling, G. B., and Thomas, E. W. P.: Treatment of Lupus Vulgaris with Calciferol, Brit. J. Dermat. **58**:45 (March-April) 1946. Treatment of Lupus Vulgaris with Calciferol, Lancet **1**:919 (June 22) 1946.

4. Feeny, P. J.; Sandiland, E. L., and Franklin, L. M.: Calciferol in Tuberculosis: Review of One Hundred and Fifty Cases of Lupus Vulgaris; Review of Twenty-One Cases of Pulmonary Tuberculosis, Lancet **1**:438 (April 5) 1947.

hospitalization was necessary, as all other forms of treatment had failed. The average duration of these cases was nineteen years. His schedules varied as follows: In 7 cases the patient received 600,000 units of calciferol twice weekly; in 7, the calciferol was in an oily solution, in capsule form, and in 6, it was given in emulsion form, the dose being 150,000 units per day. During the first two weeks, in practically all cases, the condition became worse. After the third week improvement began. In 14 cases the patients were discharged clear of lupus lesions; in 3 others they were much improved.

Charpy,[5] one of the original proponents of this therapy, advised 15 mg. of vitamin D_2 (1 mg. of vitamin D_2 is equal to 40,000 units) in alcoholic solution twice weekly for four weeks followed by the same doses for periods varying from two months to two years. He stressed that this treatment should be accompanied with 1½ pints (710 cc.) of milk daily, plenty of meat, fruits and vegetables. Fats should be taken sparingly and the intake of salt reduced. Charpy expressed the belief that the good effects should be apparent within fifteen days. If no improvement took place, failure of absorption or of tissue permeability should be suspected. In successful cases there is no doubt of the clinical benefit, although anatomic cure is more doubtful.

Dowling and Thomas [8] stated that calciferol will effect a cure in most cases. Treatment should be intensive for three months and carried on possibly for six to twelve months. They used a schedule of 150,000 units daily. Total doses varied from 9,500,000 units to 62,500,000 in adults, and 4,500,000 to 33,000,000 units in children.

Hohmann and Beening [6] reported good results without exception in 87 cases in which a schedule of 90,000 units daily for the first week, and 150,000 units daily for three months thereafter, was used.

Fromer and Piacente [7] employed the following schedule: 300,000 units every other day for the first week, 200,000 units every other day for the second week and from 50,000 to 100,000 units every day thereafter.

Other schedules have been suggested; these do not vary significantly from the aforementioned ones. All schedules have been geared to achieving maximum safe doses without significant toxicity.

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5. Charpy, J.: Massive Doses of Vitamin D_2 in Therapy of Cutaneous Tuberculosis, Ann. de dermat. et syph. **6**:310 (May-June) 1946; Ärztl. Monatshft. **2**:579 (June) 1946.

6. Hohmann, W. J., and Beening, G. W.: Massive Doses of Vitamin D_2 in Therapy of Lupus Vulgaris, Nederl. tijdschr. v. geneesk. **91**:78 (Jan. 11) 1947.

7. Fromer, J. L., and Piacente, S.: Vitamin D_2 (Calciferol) in Cutaneous Tuberculosis: Report of Seven Cases, Lahey Clin. Bull. **5**:232 (April) 1948.

Charpy [5] stressed the importance of alcoholic solution of calciferol, although the experiences of others indicate that other solvents are just as satisfactory.

The addition of calcium to the therapeutic regimen is fairly well accepted in the French reports, although Feeny [4] in England stated the belief that the average diet contains sufficient calcium. He maintained that the nutrition of the French people was deficient in calcium during the war and that therefore supplementary amounts were necessary. Only one investigator reported no striking benefit from vitamin D_2 therapy.[8]

The mode of action is unknown. Tomlinson [9] reported that in 3 cases studies of the calcium content made on specimens of tissues obtained from healed lupus skin and from normal skin showed a considerable increase in calcium content of the healed skin, as compared with the normal tissue. Charpy [5] advanced the speculation that the liberation of the phosphate ions into the skin is the effective mechanism. It is beyond the scope of this paper to enter into further theoretic discussion of this matter.

An intriguing and baffling observation in connection with treatment is that though lupus vulgaris is helped remarkably, pulmonary involvement may become activated.[10] Fortunately, this development does not occur regularly (case 2).

One additional point is in order. In the concept of cutaneous tuberculosis a wide range of lesions and some disputed cutaneous entities are included. It would be going too far afield for us to evaluate vitamin D_2 therapy in all these entities. Reports on evaluation of this therapy in actual or alleged cases of cutaneous tuberculosis are gradually appearing in the literature.[11] This report confines itself to the use of calciferol in lupus vulgaris only.

Since there is potential danger in the misuse of this treatment, a discussion of the toxic symptoms is advisable. Since benefits of treatments are thought of in long range effects, these toxic symptoms will be divided into reversible (minor) and irreversible (serious) reactions. The reversible symptoms include nausea, vomiting, gastrointestinal discomfort, anorexia, occasional diarrhea, mental depression, headache,

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8. Aitken, R., in Discussion on Vitamin D in Cutaneous Tuberculosis, Lancet **2**:398 (Sept. 13) 1947.

9. Tomlinson, K. M., in Discussion on Vitamin D in Cutaneous Tuberculosis, Lancet **2**:398 (Sept. 13) 1947.

10. Macrae.[2] Tomlinson.[9] Dowling, G. B., in Discussion on Vitamin D in Cutaneous Tuberculosis, Lancet **2**:398 (Sept. 13) 1947.

11. Fromer and Piacente.[7] Michelson and Steves.[1] Priest, R. E.: Treatment of Endonasal and Cutaneous Lupus Vulgaris with Calciferol: Report of a Successful Case, Laryngoscope **58**:305 (April) 1948.

giddiness, abnormal tiredness, some frequency of urination in association with transient albuminuria, Herxheimer-like flareup (Macrae [2]), neuralgia along the course of the mandibular nerve, tenderness of the gums and teeth and tingling of the extremities.

Macrae [2] reported two unusual reactions beginning with lacrimal and nasal discharge. Treatment was stopped immediately, but for the next three weeks symptoms were progressive. The patients became drowsy, and thereafter they manifested peripheral neuritis and went into coma. The systolic blood pressure dropped, and in 1 instance Cheyne-Stokes respiration developed. Both patients recovered completely. Interestingly enough, in 1 case the lupus lesions disappeared com-

Fig. 1 (case 1).—*A*, showing multiple areas of ulceration on the face. *B*, the patient as observed twelve months after the second course of treatment.

pletely during the toxic phase. Another unusual reversible reaction is reported in our case 3.

Metastatic calcification is the serious (irreversible) reaction which limits the dosage scheme. Fromer and Piacente [7] expressed the belief that frequent determinations of blood calcium and studies of nonprotein nitrogen at regular intervals would keep this incidence down to a minimum. Michelson and Steves [1] stated the opinion that subjective symptoms were the most valuable index of tolerance or intolerance. The concomitant administration of calcium and phosphorus and exposure to solar or ultraviolet rays augment the effect of vitamin D and may render it more toxic. In most carefully controlled cases reported, this reaction did not occur.

REPORT OF CASES

CASE 1.—M. C., a Negro woman aged 21, was first seen by us on Jan. 20, 1947. She stated that at the age of 7 she had noticed a pinhead-sized lesion on the tip of her nose. This had slowly enlarged, and after about two years ulceration took place. Soon thereafter other nodules appeared, and the glands of the neck became enlarged. Over the intervening years new nodules appeared, in association with periodic swelling of the glands of the neck. The patient stated that numerous roentgenograms of her chest had showed no abnormalities.

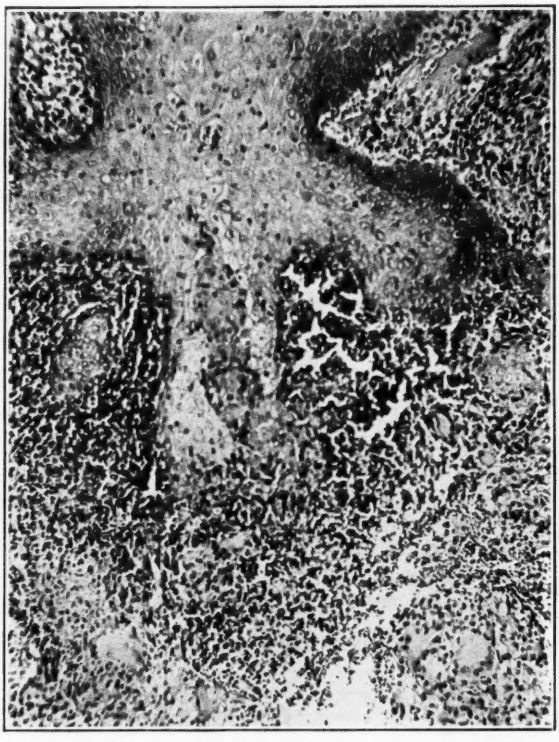

Fig. 2 (case 1).—Showing acanthosis, hyperkeratosis and infiltration consisting of lymphocytes, epithelioid cells and Langhans' giant cells; × 120.

Previous treatment had consisted of "sanatorium rest cure" and various local medications. There had been some improvement with rest after several months, but the eruption became worse soon after the patient's discharge from the hospital.

On physical examination the patient was seen to have multiple areas of ulceration on the face (fig. 1*A*). There was appreciable destruction of the nose, multiple deep ulcerations of the nasolabial folds and the lips and one area of ulceration of the inner canthus of the right eye extending partially into the eye

socket. The conjunctivas were decidedly injected. The borders of the ulcerative lesions were indurated. In the submental region there were subcutaneous masses but no ulceration or drainage.

The report on biopsy revealed the following data: The epidermis showed hyperkeratosis and acanthosis. The underlying tissue was extremely infiltrated with lymphocytes and showed dilated vessels, especially in the most superficial stratum. There were a large number of giant cells of the Langhans type and occasionally indistinct, nodular accumulations of pale epithelioid connective tissue cells. The diagnosis was lupus vulgaris (figs. 2 and 3).

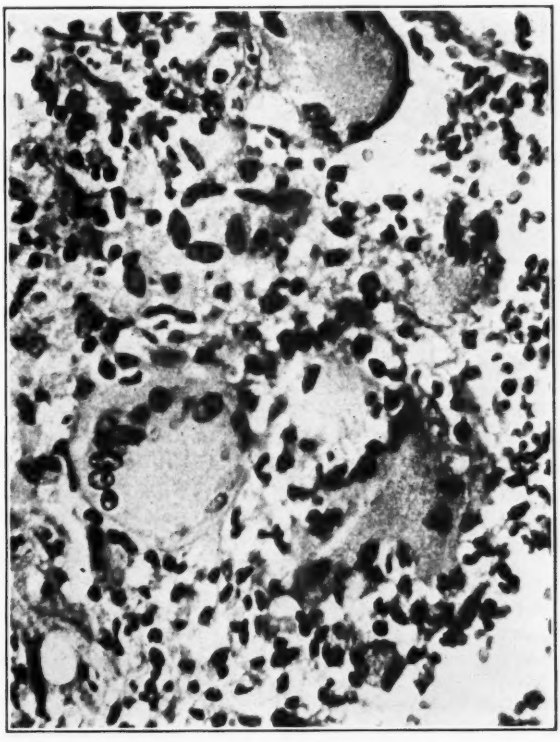

Fig. 3 (case 1).—Same section as in fig. 2, lower right corner, showing the cells in tubercle formation; × 600.

Culture of the discharge and of portions of the tissues taken from the edge of the lesions produced a growth of Mycobacterium tuberculosis on the Petronani medium.

Course.—On February 2, the patient was placed on a regimen of 150,000 units of calciferol (drisdol®) per day. In addition she was given 1.5 Gm. of calcium gluconate per day. Within one month there was a 50 per cent improvement. Treatment with calciferol was continued until June 14, at which time

only a small ulcerated area persisted on the upper lip. Six weeks later, on reexamination, there was still slight crust formation, and the patient was placed again on treatment for two months. During this time no toxic symptoms were noticed. The urine was normal on repeated examinations, and studies of the blood calcium showed normal amounts. Six months after the second course of treatment all the lesions had completely involuted and all signs of activity, including the indurated masses in the submental and anterior cervical regions, were gone. Twenty months after the second course of treatment the patient was reobserved; no signs of activity were present then (fig. 1 *B*).

CASE 2.—M. W., a Negro girl aged 15, was first seen by us on Oct. 12, 1947. She stated that two years previously she had noticed small nodules on the left cheek and on the nose. These had gradually increased in number and in size, and many of them ulcerated and discharged pus. All previous treatment had consisted of local applications, during which the process extended.

The past history revealed pulmonary tuberculosis, established by identification of M. tuberculosis in the sputum.

Examination of the skin revealed several ulcerated areas closely confluent, involving a surface of about 5 cm. in diameter on the left cheek. The borders of the lesion were indurated and the centers covered with a purulent, hemorrhagic crust. On the nose there were multiple small nodules but no ulceration. These nodules did not completely blanch on diascopic pressure. There was pronounced cervical adenopathy.

Report on Biopsy.—The epidermis was thickened and formed anastomosing rete pegs. The dermis showed congestion, edema, small areas of hemorrhage and focal infiltration of lymphocytes and neutrophils. One area contained a circular group of epithelioid cells and lymphocytes. This lesion resembled an early tubercle. The diagnosis was chronic dermatitis, probably tuberculosis.

Cultures from the tissue grew no organisms. A roentgenogram of the chest showed mottled infiltration radiating from both hilar regions throughout the midportion of the lung fields. No cavitation was present.

Course.—The patient was started on treatment with calciferol (drisdol®) in October, the treatment consisting of 150,000 units per day in addition to 1 quart (0.95 L.) of milk. Within one week the lesions showed some signs of involution, and within three weeks most of the drainage had ceased. Within six weeks of treatment the lesion was completely dry. Interestingly enough the use of milk was discontinued for the next few weeks, and it was thought by several independent observers that the rate of involution was slower than usual. Milk was reintroduced into the diet and calciferol continued till January 1948, at which time the lesion was 90 per cent involuted.

Although the patient showed no toxic symptoms, the blood calcium content in January 1948 was reported as 12.5 mg. per hundred cubic centimeters. Repeated urinalyses revealed normal urine. Roentgenologic study revealed no essential change in the pulmonary findings. When the patient was seen three months after treatment, involution had proceeded even further, and only a few nodules persisted. When she was seen twelve months later, the eruption appeared clinically inactive.

CASE 3.—S. G. R., a Negro aged 20, was first seen by us on May 5, 1948, at which time he stated that he had lesions of the face of six months' duration. These had begun as small "lumps," which later became ulcerated and discharged considerable amounts of thick pus. Previous local treatment had been ineffective.

The patient also stated that in 1944 he had had an anterior cervical adenitis, for which he had been treated at the Johns Hopkins Hospital. He had been told that this condition was tuberculous. The adenopathy had subsided in about three months, with considerable scar formation.

Early in 1948 he had been told by a physician that he had secondary syphilis. He had been given five intravenous injections at the time.

On examination the patient was seen to have several areas of ulceration on the inner canthus of the eyes, extending medially to the bridge of the nose.

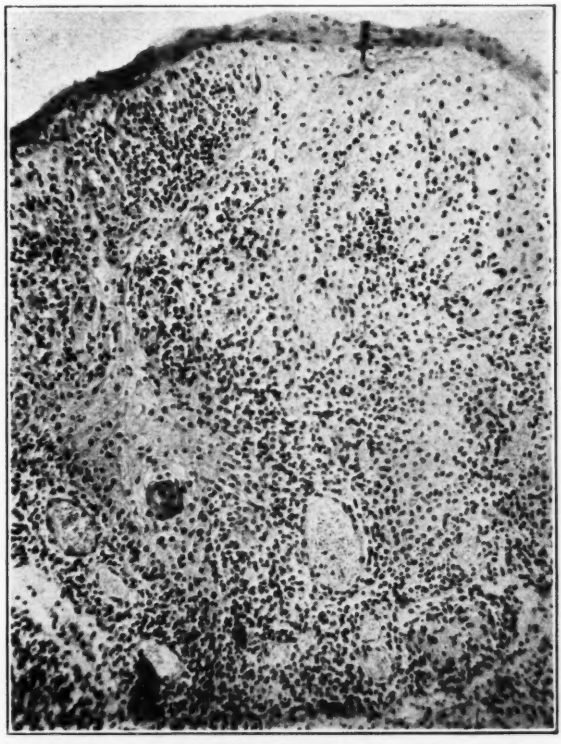

Fig. 4 (case 3).—Showing infiltration consisting of lymphocytes, occasional Langhans' giant cells and epithelioid cells; × 120.

There were two similar lesions of the right cheek. The borders of the ulcerations were quite indurated, and those of the inner canthus extended partly into the eye socket.

Report on Biopsy.—The skin showed decided acanthosis and hyperkeratosis of the epithelium. In the underlying tissue there were nodules consisting of giant cells with peripheral arrangement of the nuclei and a number of epithelioid cells. Some of the giant cells presented vacuoles. There were numerous lymphocytes and occasional plasma cells in the surrounding area (figs. 4 and 5).

The diagnosis was lupus vulgaris.

Numerous roentgenologic examinations of the chest revealed no abnormalities. Cultures grew no organisms; observations on urinalysis were repeatedly normal. Serologic tests for syphilis revealed low positive titers of 2 to 4 Kahn units on several occasions. Examination of spinal fluid on June 6 showed no abnormalities.

Course.—Because of the history of previous inadequately treated syphilis the patient was given penicillin therapy consisting of 50,000 units every two hours for thirteen days, beginning on May 5. This therapy had no effect on the lesions. On May 21, the patient was placed on calciferol therapy and also given 1.5 Gm. of calcium gluconate. He received this treatment until June 13. On

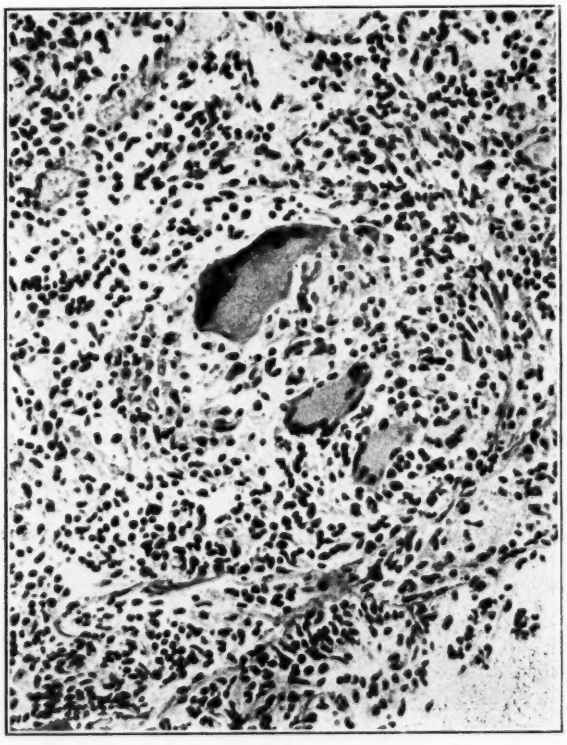

Fig. 5 (case 3).—Showing lymphocytes, plasma cells, Langhans' giant cells and epithelioid cells in tubercle formation; × 600.

that date his temperature was elevated to 102 F. This elevation persisted intermittently for several days. The patient began to complain of pain in the right lumbar region, radiating to the right shoulder. There was no cough or sputum formation. The blood calcium on June 9 was 12 mg. and on June 10 11.5 mg. per hundred cubic centimeters. Repeated daily urinalyses were normal at this time. The white blood cell count was 22,000, with polymorphonuclear cells, 81 per cent; lymphocytes, 15 per cent, and eosinophils, 4 per cent.

The patient was sent to the Eastern North Carolina Sanatorium for further study. No evidence of tuberculosis other than the cutaneous lesions could be

established by physical examination and by roentgenologic studies. The febrile reaction subsided after several days. The cutaneous lesions continued to involute, so that by August 19 they were regarded as completely healed. Because of this unusual reaction no further calciferol will be given unless reactivation takes place. The possibility of a delayed reaction to penicillin was not completely eliminated.

COMMENT

A review of 3 cases of lupus vulgaris in which calciferol (vitamin D_2) therapy was used indicates that this form of treatment is probably one of the most effective for this infection. That it is not free from potentially serious reaction is self evident. Moreover, it must be used with caution in the presence of active pulmonary tuberculosis.

A word of discussion concerning streptomycin is in order. While both streptomycin [12] and calciferol are effective remedies, the eventual choice of one or the other forms of treatment will depend primarily on which produces more serious toxic irreversible reactions in therapeutically effective schedules. Other minor factors, such as the cost of treatment, its duration and the need for hospitalization, may have to be considered. Hospitalization is not necessary with calciferol therapy. The optimum dosage, which will produce the best therapeutic results with the least toxicity has not been established for either streptomycin or calciferol. Possibly a combination of both forms of therapy may be additive or synergistic,[13] thereby combining the desired therapeutic advantage with reduction of dose and toxicity. As a rule, in the presence of concomitant pulmonary tuberculosis the use of streptomycin should precede that of calciferol in the treatment of cutaneous tuberculosis.

CONCLUSIONS

1. Vitamin D_2 (calciferol) in doses of 150,000 units per day caused involution of lesions in 3 cases of lupus vulgaris.

2. Supplementary treatment with calcium may enhance this effect.

3. In the presence of active pulmonary tuberculosis this medication should be used cautiously. That the presence of active pulmonary tuberculosis is not an absolute contraindication to the use of vitamin D_2 is supported by the report of case 2, in which no flare-up of proved pulmonary tuberculosis took place under active treatment with calciferol.

4. Careful, repeated examinations should be made during the course of therapy for serious (irreversible) effects of metastatic calcification.

708 Medical Arts Building (10).

12. O'Leary, P. A.; Ceder, E. T.; Hinshaw, H. C., and Feldman, W. H.: Treatment of Various Types of Cutaneous Tuberculosis with Promizole and Streptomycin, Arch. Dermat. & Syph. **55**:222 (Feb.) 1947.

13. Cornbleet, T.: Combined Calciferol and Streptomycin in Lupus Vulgaris, J. A. M. A. **138**:1150 (Dec. 18) 1948.

Clinical Notes

A STRANGE CASE OF PALATITIS

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A NEW clinical experience is always stimulating and as such should be shared with one's colleagues. It is in that spirit that I record the following case.

For quite some time I had been observing a comely young woman for soreness of the roof of the mouth. Although never severe, it was at all times bothersome, particularly so during the menstrual periods when invariably the symptoms were aggravated. Examination showed that her complaint was due to an inflammatory patch on the hard palate—a rather well circumscribed patch about 3 cm. in diameter, slightly edematous, and studded with punctate hemorrhages. It was only slightly tender to touch.

I had never before observed a lesion quite like it, nor could I fit it into any definite dermatologic category—except to suspect that it was due to irritation of some sort. The history, however—and a rather exhaustive history, I thought—failed to reveal any clews. Then, too, the clinical exacerbations coincided each time with the onset of menses. Throughout this period she was also in frequent consultation with her internist for a train of symptoms which he considered were due to psychosomatic rather than to organic disease, for complete and repeated laboratory studies, roentgenologic and clinical examinations had failed to reveal anything abnormal other than the inflammatory patch on the palate.

Treatment with a soothing preparation for use as a mouthwash, a diet of bland and soft foods and sedation afforded only slight relief. Hormonal therapy, instituted on an empiric basis, was also without benefit. A clinical test ruled out the possibility of a fixed drug eruption, and, finally because the case had taxed whatever ingenuity I could muster, it was suggested that a biopsy be performed with the hope that a histologic study would be of some help. The young woman overheard the suggestion to her physician and heard me repeat that I still held the opinion that the lesion was a simple inflammatory reaction such as might result from trauma. It was then—when the term "trauma" was used instead of irritation—that she asked whether the lesion might not be due to fellatio, only she spoke in the vernacular. The menstrual exacerbations? She had practiced the art only during the menstrual periods.

The biopsy, of course, was deferred and subsequent events proved how right she was. The lesion healed in due course, and then, possessed of a highly developed sense of curiosity—she actually reproduced the lesion.

I have since wondered on many occasions whether to be proud of or chagrined at my naivete and failure to solve the case until I encountered a zestful report in the French literature of another case which had similarly puzzled the physician. It is quoted in Ronchese's interesting monograph, "Occupational Marks."[1] In my patient, however, the lesion was avocational—I believe.

104 South Michigan Avenue.

1. Ronchese, F.: Occupational Marks and Other Physical Signs: A Guide to Personal Identification, New York, Grune & Stratton, Inc., 1948, p. 167.

MULTIPLE SQUAMOUS CELL CARCINOMA OF THE SKIN ASSOCIATED WITH CHRONIC LYMPHATIC LEUKEMIA

Observations on the Effect of Urethane Therapy

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In 1941 Engelbreth-Holm[1] reviewed 22 cases of leukemia associated with other malignant conditions and added reports of 11 cases of his own. Since then 13 additional cases[2] of leukemia combined with various types of malignant diseases have been reported.

Of the 46 cases reported, carcinoma of the skin was associated with the leukemia in 14.[3] Basal cell carcinoma was reported in 8 and squamous cell carcinoma in 6 of the cases. Chronic lymphatic leukemia was noted in each of the 14 cases.

We have observed a patient who exhibited multiple squamous cell carcinoma of the skin associated with chronic lymphatic leukemia. We report this case because of apparent rarity of the combined malignant conditions and also because this patient received urethane therapy and showed clinical and hematologic response, as well as definite changes in a squamous cell carcinoma of the skin,

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From the Departments of Medicine and Pathology, Wayne University College of Medicine and the City of Detroit Receiving Hospital.

1. Engelbreth-Holm, J.: Leukemia and Another Malignant Tumor in Same Patient, Nord. med. (Hospitalstid.) **9**:791-799, 1941.

2. (*a*) Morrison, M.; Feldman, F., and Samwick, A. A.: Carcinoma and Leukemia: Report of Two Cases with Combined Lesions; Review of Literature, Ann. Int. Med. **20**:75-84, 1944. (*b*) Dustin, P., Jr.: Coexistence d'une leucémie lymphöide et d'un carcinome gastrique, Rev. belge sc. méd. **13**:199-208, 1941. (*c*) Delcourt, R., and van Vliet, P.: Coexistence d'une leucémie lymphöide et d'un carcinome, Acta med. Scandinav. **119**:47-56, 1944. (*d*) Evans, T. S.; Swirsky, M. Y., and Chernoff, H. M.: Primary Endothelioma of the Pleura: Report of a Case in a Patient with Chronic Lymphatic Leukemia, Ann. Int. Med. **24**:262-272, 1946. (*e*) Reiss, F., and Konheim, W.: Basal Squamous Cell Epithelioma Associated with Leukemia, Arch. Dermat. & Syph. **55**:507-511 (April) 1947.

3. (*a*) Engelbreth-Holm.[1] (*b*) Reiss and Konheim.[2e] (*c*) Fuhs, H.: Multizentrische Basalzellenepitheliome bei lymphatischer Leukämie, Dermat. Wchnschr. **85**:1533, 1927. (*d*) Scheuffler, A.: Carcinombildung auf einem Leukämid, Arch. f. Dermat. u. Syph. **168**:586-596, 1933. (*e*) Schreiner, B. F., and Wehr, W. H.: Cancer Associated with Leukemia, Am. J. Cancer **21**:368-371, 1934. (*f*) Pulvertaft, R. J. V.: Multiple Primary Epithelioma in Lymphatic Leukemia, Brit. J. Surg. **24**:50-54, 1936.

which occurrences may be attributed to the urethane therapy. The clinical and hematologic responses to urethane therapy are reported in detail elsewhere.[4]

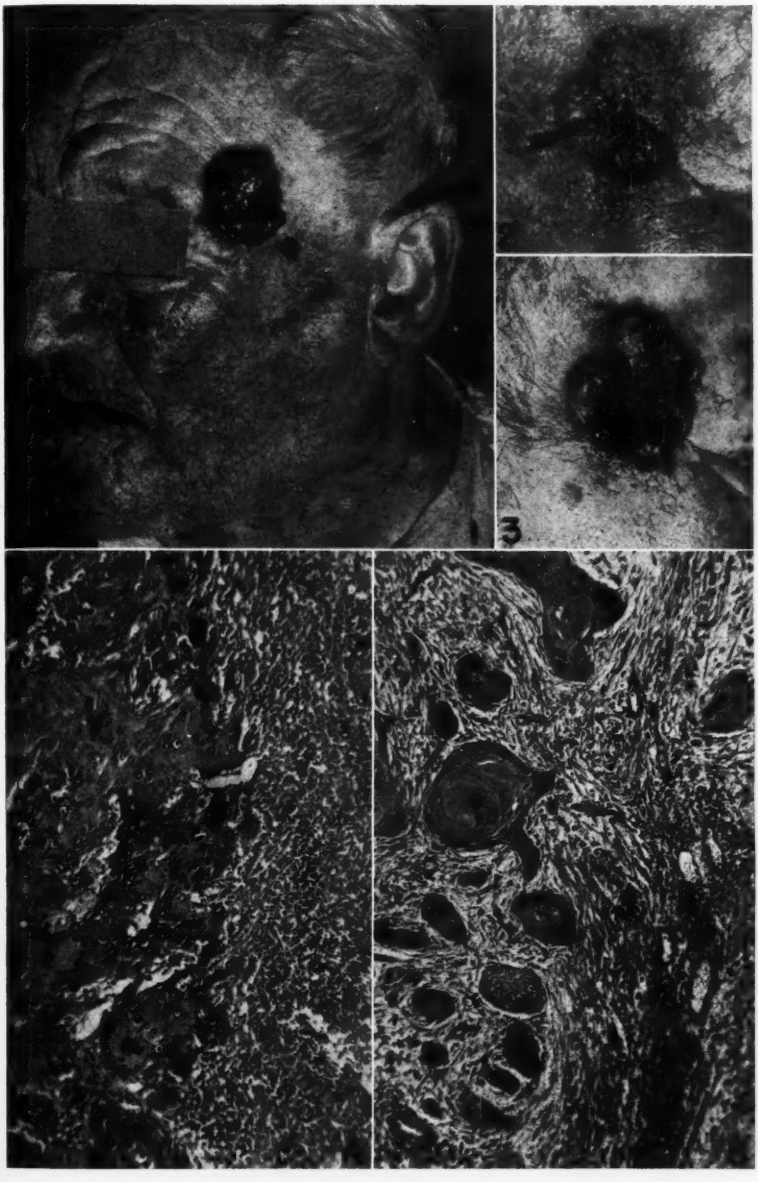
REPORT OF A CASE

H. G., a 76 year old white man, was admitted to the hospital because of the appearance and rapid growth of three tumors about the face and forehead and a fifteen year history of massive, progressive enlargement of masses in the cervical, axillary and inguinal regions. The patient was well developed, fairly well nourished and not particularly uncomfortable. On one side of the nose there was an elevated, ulcerated lesion 1.5 cm. in diameter, with a pearly circular border (figure, *1*). Over the left temporal region there was a papillary mass 4 cm. in diameter, with a completely ulcerated and hemorrhagic surface (figure, *1*). Over the right temporal region there was an indurated, fungating tumor 3 cm. in diameter, in the center of which was a small superficial ulcer (figure, *2*). There were matted lymph nodes in both sides of the neck. Axillary, inguinal and supraclavicular nodes varied from 2 to 5 cm. in diameter. The edge of the liver was 4 cm. below the right costal margin, and that of the spleen was at the level of the iliac crest. The tumors of the skin over the left temporal region and near the nose were removed surgically, and the large tumor over the right temporal region was subjected to biopsy. All three neoplasms proved to be squamous cell carcinoma. Biopsy of an axillary lymph node and study of the blood and bone marrow established the diagnosis of chronic lymphatic leukemia.

Oral urethane therapy was started with 3 Gm. doses daily. Two weeks after onset of treatment the patient began to experience anorexia, but there was no nausea or vomiting. After the patient had received 71 Gm. of urethane, the leukocyte count, which had been originally 126,500 per cubic millimeter, became less than one-third its initial value. There was a reduction in the sizes of the enlarged lymph nodes and spleen. The dose of urethane was increased to 6 Gm. per day, and this amount was well tolerated. After 191 Gm. of urethane had been administered, vomiting occurred after ingestion of the drug. This was obviated by reducing the dose to 3 Gm. daily.

During the first fourteen days of treatment a circular zone of hyperemia appeared in the skin around the edge of the tumor in the right temporal region. After 107 Gm. of urethane had been given, a small area of necrosis developed in this tumor at the site of the incision made when the specimen had been removed for biopsy. As treatment was continued, the necrosis extended until it ultimately involved the entire surface of the tumor. The superficial one third to one half of the tumor sloughed off. In the meantime there was no lateral extension of the lesion (figure, *3*). Successive biopsies revealed changes in the histologic appearance of the tumor, as described later. Treatment was discontinued after 221 Gm. of urethane had been given because the patient refused further hospitalization. The residual portions of the cutaneous tumor were removed surgically before the patient left the hospital. Three weeks after therapy had been discontinued the patient died of coronary thrombosis.

4. Berman, L., and Axelrod, A. R.: Effect of Urethane on Malignant Diseases: Clinical, Hematologic and Histologic Observations on Patients with Carcinoma, Leukemia and Related Diseases [case 6], Am. J. Clin. Path. **18**:104-129, 1948.



1, an elevated, ulcerated lesion on one side of the nose and a papillary mass over the left temporal region. *2*, a small, superficial ulcer. *3*, changes observed in the tumor in the right temporal region. *4*, photomicrograph of a specimen taken before the beginning of treatment. *5*, photomicrograph of specimen obtained after the administration of 221 Gm. of urethane.

Histologic Study.—Biopsy of a specimen taken from the edge of the tumor before treatment began showed the growth to be a well differentiated squamous cell carcinoma with pronounced cornification of the epithelial masses. The advancing margin of the tumor was composed of irregular masses of epithelial cells in squamous arrangement with relatively less cornification. The tumor infiltrated and replaced the connective tissue of the derma. There was little evidence of reaction in the adjacent connective tissue, which was infiltrated with small lymphocytes (figure, *4*). There were a few small leukemic nodules in the outer portions of the derma beneath the normal squamous epithelium. The second specimen was obtained after 221 Gm. of urethane had been administered. The advancing margin of the tumor was broken up into irregular, small masses of epithelium separated by abundant, recently formed connective tissue stroma. The stromal reaction extended slightly beyond the edge of the tumor (figure, *5*).

COMMENT

The low incidence of the association of leukemia with other malignant changes was noted by Schreiner and Wehr,[3e] who observed only 4 such cases among a total of 11,212 cases of malignant conditions, including 90 cases of leukemia.

The association of chronic lymphatic leukemia with carcinoma of the skin appears to be greater than would be anticipated, as was pointed out by Engelbreth-Holm.[1]

The change in the histologic appearance of the squamous cell tumor, characterized by the development of abundant, newly formed fibroblastic stroma, appeared unusual for this type of tumor and was similar to the change produced by urethane in the structure of the Walker rat carcinoma. Haddow and Sexton[5] reported that under the influence of urethane the characteristic cellular texture of the Walker carcinoma gave place to a more fibrous structure, with spindle cells and a distinctly more abundant stroma. They expressed the opinion that the change was due in part to involvement of vessels and stroma. For these reasons we consider the similar alteration in the squamous cell carcinoma of the skin a possible effect of urethane.

SUMMARY

A case of multiple squamous cell carcinoma of the skin associated with chronic lymphatic leukemia is reported. In the course of urethane therapy degenerative changes were noted in a squamous cell carcinoma of the skin. These were characterized by necrosis, with sloughing of the superficial part of the tumor and a decided increase of the fibroblastic stroma without lateral extension of the mass. The possible relation between these changes and urethane therapy is discussed.

Wayne University College of Medicine.

5. Haddow, A., and Sexton, W. A.: Influence of Carbamic Esters (Urethanes) on Experimental Animal Tumours, Nature, London **157**:500-503, 1946.

AUREOMYCIN IN MOLLUSCUM CONTAGIOSUM

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Experimental work of Wile and Kingery [1] on the etiology of molluscum contagiosum led them to conclude that the disease is due to a filtrable virus. Further reports on the value of the drug aureomycin in diseases of the rickettsia-virus group led us to try it on a widespread case of molluscum contagiosum.

C. S. presented himself in our office with a generalized eruption of molluscum contagiosum, with what we estimated to be three hundred lesions on the trunk and extremities. There was a history of the appearance of a dozen or so lesions on the trunk at first, and of the condition's becoming generalized a few days after a massage in a Turkish bath. A few of the lesions were curetted, more for diagnostic purposes than for any other, because it seemed hopeless to try to treat so many lesions by this method.

We prescribed aureomycin, 250 mg. twice a day by mouth for two days. Four days after treatment with the drug had been stopped, the lesions were almost flat. No more aureomycin was prescribed, but white lotion N.F. was prescribed to be applied locally to hasten the removal of the remaining debris in the lesions. In another week nothing was left of the lesions but pigmented macules, and in the following week there was no sign of recurrence.

This dramatic response, although in only a single case, seemed to justify calling attention to the possibility of using this drug in molluscum contagiosum and in other conditions presumably of virus origin, such as verruca vulgaris, juvenile flat warts and plantar warts.

7026 Jenkins Arcade (22).

From the Department of Dermatology and Syphilology, University of Pittsburgh School of Medicine.

1. Kingery, L. B.: Histogenesis of Molluscum Contagiosum, Arch. Dermat. & Syph. **2**:144 (Aug.) 1920.

CONTROL OF PRURITUS WITH DIPHENHYDRAMINE (BENADRYL®) HYDROCHLORIDE OINTMENT

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Pruritus, or itching, is a distressing symptom of many dermatoses. In clinical management of pruritus, optimal therapeutic results are predicated on adequate diagnosis of the etiologic factor. Briefly, the various types [1] of pruritus may be classified, according to cause, under three main headings:

1. Pruritus incident to parasitic diseases of the skin, such as scabies and pediculosis. Destruction of the parasite by use of suitable antiparasitic agents will automatically clear up the pruritus.

1. Klauder, J. V.: Pruritus: Considerations on Its Pathogenesis, Pennsylvania M. J. **37**:729 (June) 1934. Sulzberger, M. B., and Wolf, J.: Pruritus and Its Treatment, M. Clin. North America **19**:971 (Nov.) 1935.

2. Pruritus associated with systemic diseases, such as diabetes mellitus and jaundice. Treatment of the underlying systemic disease will help control the pruritus.

3. Pruritus due to allergy and caused by release of histamine or H substance in the tissues. In this group are urticaria, atopic dermatitis and contact dermatitis, as well as localized neurodermatitis and localized areas of pruritus. Only H substance–mediated pruritus is considered in this report.

Oral use of antihistaminic agents for various forms of allergy is now well established.[2] Although the therapeutic action of these agents is purely palliative, they afford significant symptomatic relief. In the cutaneous manifestations of allergy, peroral antihistaminic therapy has been found particularly useful for symptomatic control of itching incident to urticaria, atopic dermatitis and contact dermatitis.

It has been demonstrated by other workers in the field of allergy[3] that local application of a solution of an antihistaminic agent produces significant reduction in the whealing reaction produced by application of histamine to the skin. However, oral administration of the antihistaminic agent has but a slight inhibitory effect on experimentally produced histamine wheals. This observation suggests that local application of an antihistaminic substance should be more effective than oral administration in inhibiting histamine wheals.

Wheals resulting from an antigen-antibody reaction, such as those occurring in persons sensitive to ragweed, are similarly inhibited by local application of a solution of an antihistaminic agent. This fact would suggest that the antigen-antibody reaction leads to release of histamine in the tissues and that antihistaminic solution inhibits the effects of histamine.

The mode of action of antihistaminic agents is not definitely known. Several theories have been proposed: that they prevent the release of histamine in tissues, that they neutralize histamine and that they block the action of histamine. The last theory is accepted by most authorities. It is claimed that the antihistaminic drug combines with the tissue cells at the site of action of the histamine rather than with the histamine itself. Thus, the pharmacologic effects of histamine are prevented by blocking the union of histamine with the tissue cells.

With these considerations in mind, it was felt that incorporation of diphenhydramine hydrochloride (benadryl hydrochloride®), an antihistaminic agent, in an ointment would permit concentration of this therapeutic agent in the epidermis, where its histamine-blocking powers would be of great value. Symptoms resulting from allergic release of histamine in the tissues, such as pruritus and exudation of fluid, might thus be controlled or eliminated.[4]

Another advantage from the local application of an antihistaminic agent, in the form of diphenhydramine hydrochloride ointment, would be elimination of systemic side actions, such as drowsiness and nausea, that may accompany the oral administration of antihistaminic substances.

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2. Levin, S. J.: β-Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl): Its Use in Allergic Diseases, J. Allergy **17**:145 (May) 1946.

3. Friedlaender, S., and Feinberg, S. M.: Histamine Antagonists: III. The Effect of Oral and Local Use of β-Dimethylaminoethyl Benzhydryl Ether Hydrochloride on the Whealing Due to Histamine, Antigen-Antibody Reactions, and Other Whealing Mechanisms: Therapeutic Results in Allergic Manifestations, J. Allergy **17**:129 (May) 1946.

4. Feinberg, S. M., and Bernstein, T. B.: Tripelennamine ("Pyribenzamine") Ointment for the Relief of Itching, J. A. M. A. **134**:874 (July 5) 1947.

Accordingly, diphenhydramine hydrochloride ointment, containing 2 per cent of the drug, was employed in management of the following dermatoses in which itching is a prominent symptom: neurodermatitis (generalized and localized), contact dermatitis, nummular eczema, stasis eczema, pruritus ani, pruritus vulvae and pruritus scroti.

Clinical results are summarized in the accompanying table.

COMMENT

In a series of 268 patients with various pruritic dermatoses, 196 had some relief of itching when diphenhydramine hydrochloride ointment was applied locally, while 72 had no improvement. In this series, improvement is defined as relief of itching, evaluation being based on the patient's own statement. It is not implied that the underlying condition of the skin cleared up as a result of local application of diphenhydramine hydrochloride ointment.

Clinical Results with Diphenhydramine Hydrochloride (Benadryl Hydrochloride®) Ointment in Control of Pruritus

Conditions	No. of Patients	No. of Patients Showing Improvement	No. of Patients Not Showing Improvement
Neurodermatitis			
Generalized	32	19	13
Localized	70	58	12
Contact dermatitis	51	36	15
Nummular eczema	22	17	5
Stasis eczema	18	14	4
Pruritus ani	20	15	5
Pruritus vulvae	10	8	2
Pruritus scroti	7	5	2
Miscellaneous dermatoses	38	24	14
Totals	268	196	72

In some cases, the ointment had to be applied every two or three hours in order to control the pruritus. With relief of pruritus, there was, of course, decreased scratching and excoriation and less mechanical injury to the skin. This situation usually resulted in objective improvement in clinical manifestations of the dermatoses, particularly in cases of localized neurodermatitis and stasis eczema.

In neurodermatitis disseminata, or atopic eczema, which is a recurrent, resistant, pruritic dermatosis, there was relief of pruritus for 19 of 32 patients treated. However, some of these patients who showed relief of pruritus had exacerbations of the atopic eczema while under treatment with diphenhydramine hydrochloride ointment. The ointment apparently had no effect on the course of atopic eczema.

In localized neurodermatitis, of 70 patients treated, 58 showed improvement and relief of pruritus. These patients can also be classified as having lichen chronicus simplex. As is well known, pruritus is an outstanding symptom in this disease, and the patient often scratches himself during the night, thus reactivating the lesions over periods of months and years. By relieving the pruritus in these cases, the vicious cycle is broken, and the patient refrains from scratching. Lesions of several years' duration have cleared up in from four to five weeks under treatment with diphenhydramine hydrochloride ointment. Some patients, however, have

had recurrences of the localized patches of neurodermatitis, either in the same or in new locations, after a lapse of from four to six months.

In contact dermatitis, of 51 patients treated, 36 experienced some relief of itching while under treatment with diphenhydramine hydrochloride ointment, while 15 patients showed no improvement or became worse. It was found that in cases of acute contact dermatitis, when the skin was highly inflamed, swollen and oozing, the patients complained of a burning sensation when the ointment was first applied. This burning sensation usually persisted in the acute cases, and use of the ointment had to be discontinued. In the milder and subacute cases of contact dermatitis, the burning sensation was less severe and was usually followed by a sensation of numbness and later by relief of itching. It was felt, therefore, that during the acute phase of a contact dermatitis conservative measures, such as wet dressings and soothing lotions and ointments, should be used. Later, after the acute phase has subsided, one may apply diphenhydramine hydrochloride ointment. In the majority of cases of contact dermatitis, however, the patients experienced considerable relief of pruritus after the application of diphenhydramine hydrochloride ointment.

Nummular eczema may be favorably influenced by the use of the ointment, which simply relieves the pruritus but has no effect on the course or progress of the disease itself. New patches of nummular eczema or reactivation of healing lesions may occur while patients are under treatment with diphenhydramine hydrochloride ointment.

The ointment is also of value in stasis dermatitis. It helps to control the pruritus. However, unless measures are used to improve the circulation in the legs, the pruritus and excoriations recur when use of diphenhydramine hydrochloride ointment is discontinued.

This ointment was found of considerable value in relieving pruritus in a group of patients with pruritus ani, pruritus vulvae and pruritus scroti. These conditions are distressing and annoying to the patient, keeping him awake at night. The diphenhydramine hydrochloride ointment, therefore, was useful in controlling pruritus in these cases. Of course, if the pruritus is due to a local cause, such as a fungous infection, it should be treated accordingly.

Diphenhydramine hydrochloride ointment was also used locally in treatment of a group of miscellaneous pruritic dermatoses, such as lichen planus, pityriasis rosea and chronic recurrent urticaria. The results were satisfactory in a majority of cases of these conditions, the patients experiencing some relief of the pruritus. Diphenhydramine hydrochloride ointment was, of course, used as a purely palliative measure in all the cases.

In a small percentage of cases, about 2 per cent of the cases in this series, signs of sensitization or irritation appeared during treatment with the ointment. The ointment was, of course, discontinued when signs of irritation developed from its use.

SUMMARY

Diphenhydramine hydrochloride ointment is of value for relief of pruritus in a variety of dermatoses.

Its action is purely palliative. It has no effect on the course or progress of a dermatosis except for relief of the pruritus.

Diphenhydramine hydrochloride ointment is worth a trial in all cases of pruritic dermatoses that have either an allergic or a neurogenic background.

Use of the ointment is contraindicated in denuded and weeping areas, because of its burning effect.

In diphenhydramine hydrochloride ointment, physicians have another means of controlling pruritus. This medication should be of especial assistance to those who treat patients with dermatologic disease.

The diphenhydramine hydrochloride ointment, with a 2 per cent concentration of diphenhydramine hydrochloride, used in this study was supplied by Parke, Davis and Company's Department of Clinical Investigation.

914 Maccabees Building.

MOLLUSCUM CONTAGIOSUM OF THE SCALP

Report of Two Cases

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White [1] and Nicoletti [2] each reported a case of molluscum contagiosum located exclusively on the scalp, and the latter, after a thorough review of the literature, collected 5 similar cases. To this small number the following observations are added.

REPORT OF CASES

CASE 1.—*History.*—D. J., an unmarried white woman aged 55, was first seen by us on Feb. 26, 1947. She complained of a small lesion situated on the vertex of the scalp, to the left of the midline, which had been present for several months and had gradually increased in size. On several occasions, while combing her hair, she had struck the lesion, causing bleeding. This development was followed by moderate tenderness for a few days.

Examination.—At the time of the initial visit, a pea-sized, round, waxy nodule with a rolled border and central hemorrhagic crust was observed in the left parietal region. A tentative diagnosis of basal cell carcinoma was made. The lesion was excised, and the specimen was submitted for biopsy. The pathologic diagnosis was molluscum contagiosum.

Treatment and Subsequent Course.—One week later, a well circumscribed, semiglobular nodule with a rolled border and depressed central plug was noted 2 cm. posterior to the original lesion (fig. 1). Microscopic examination of the expressed contents of the lesion revealed molluscous bodies. The rest of the skin was normal at that time.

This lesion, as well as two small lesions which appeared two weeks later, was destroyed by electrodesiccation. The patient was then instructed to take sulfa-

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1. White, C.: Molluscum Contagiosum of the Scalp, Arch. Dermat. & Syph. **21**:180 (Feb.) 1930.

2. Nicoletti, V.: Mollusco contagioso localizzato esclusivamente al cuoio capelluto, Arch. ital. di dermat., sif. **6**:194, 1930.

pyridine, 1 Gm. twice a day for five days, in order to prevent recurrence. Reexamination six weeks later showed the scalp to be entirely free of lesions.

CASE 2.—*History.*—W. A. E., a married white man aged 50, was seen in the office of Dr. John G. Downing on May 5, 1947. He complained of numerous lesions scattered over the entire surface of the scalp; these had been present for two months. There were no subjective symptoms, and the patient was chiefly concerned with the unsightly appearance of the lesions.

Fig. 1 (case 1).—Isolated lesion of molluscum contagiosum.

Examination.—Several hundred semiglobular lesions, varying in size from 1 to 5 mm., were seen scattered over the entire surface of the scalp. Some of the lesions were umbilicated, but the majority had a smooth, dome-shaped surface (fig. 2). The lesions occurred both singly and in groups, those in groups favoring the parting of the hair. The lesions did not extend beyond the hair line. The rest of the skin was normal. A specimen was removed for biopsy, and the histologic diagnosis was molluscum contagiosum.

Treatment and Subsequent Course.—Sulfapyridine, 1 Gm. three times a day for one week, was administered orally but failed to influence the lesions. A 25

per cent alcoholic solution of resin of podophyllum was then applied locally. This treatment caused great discomfort, without producing beneficial results, and was discontinued after two weeks. The lesions were destroyed by electrodesiccation at subsequent visits. Examination six months later showed a normal scalp.

Fig. 2 (case 2).—Multiple lesions with tendency to group formation.

SUMMARY AND CONCLUSIONS

Two cases of molluscum contagiosum, in both of which small, discrete, semiglobular lesions were located exclusively on the scalp, are reported. Treatment by excision and electrodesiccation produced beneficial results.

The occurrence of molluscum contagiosum on the scalp may be more frequent than was formerly suspected and merits consideration in differential diagnosis of tumors of the scalp.

520 Commonwealth Avenue.

AUTOHEMOTHERAPY OF HERPES ZOSTER

Results in One Hundred and Fifty-Four Cases

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Spectacular relief of pain following autohemotherapy in herpes zoster was reported by Jack W. Jones and Herbert S. Alden.[1] Cures were obtained with one injection in most cases, and 1 instance is reported in which pain subsided before the patient returned home, 75 miles from Atlanta. Jones and Alden did not report the number of patients treated, nor did they report treatment failures.

Most textbooks[2] do not mention this type of treatment. Instead, a general hodgepodge of remedies is given, these including even the use of cathartics. Becker and Obermayer[3] devoted one sentence to autohemotherapy in their textbook.

Ravaut[4] introduced injections of whole blood from vein to muscle in 1913. Centrifuged serum had been used prior to this report.

Burgess[5] attempted to draw conclusions as to the explanation of the mechanism of action of autohemotherapy. However, no clearcut explanation has ever been offered. Autohemotherapy has been my routine office procedure to the exclusion of all other treatment. Consequently, the results obtained in 154 cases are reported.

RESULTS OF AUTOHEMOTHERAPY

Data concerning only those patients with pain and active vesicles are included in this report. Asymptomatic persons were not treated. Twenty-seven patients received only one injection; 21 received two injections; 77 received three injections, and 16 received four injections.

These 141 patients averaged 2.5 injections and obtained complete relief of pain in 5.22 days, although severe pain had usually subsided before the second or third injection was given. The youngest patient treated was 4 years and the oldest, 82 years of age.

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1. Jones, J. W., and Alden, H. S.: South. M. J. **30**:735 (July) 1937.

2. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939. Andrews, G. C.: Diseases of the Skin, ed. 2, Philadelphia, W. B. Saunders Company, 1938.

3. Becker, S. W., and Obermayer, M. E.: Modern Dermatology and Syphilology, Philadelphia, J. B. Lippincott Company, 1940.

4. Ravaut, P.: Ann. de dermat. et syph. **4**:292, 1913.

5. Burgess, N.: Brit. J. Dermat. **44**:124 (March) 1932.

Injections (10 to 15 cc.) were given every third day until relief of pain was reported by the patient. Local treatment with solution of boric acid and 2 per cent phenol in calamine lotion was prescribed for most cases. Ointment containing dibucaine (nupercaine®) hydrochloride or tetracaine (pontocaine®) hydrochloride was used for hyperesthesia.

There were 4 patients who continued to have some degree of pain after autohemotherapy. These were given posterior pituitary injection U. S. P. (pituitrin®), a preparation containing the vitamin B complex, sodium iodide and roentgen therapy. They became free from pain in seventeen, twenty-six, twenty-seven and thirty-four days.

These 4 patients represent less than 3 per cent of the total group treated. All showed improvement and no longer complained of severe pain, but, because of residual dull, aching pain, autohemotherapy was stopped. Two of the 4 were in severe tension states at the onset of the zosteric pain. In fact, it is surprising that I did not encounter enough psychoneurotic persons and "complaining type" of patients in general to make the number of treatment failures run much higher in this series. When 141 patients are treated for any medical condition the treatment failures are usually more than 3 per cent simply because some patients refuse to admit a cure.

COMBINED TREATMENT

In 1937 posterior pituitary injection was used in conjunction with autohemotherapy. A series was started to compare this type of treatment with that with posterior pituitary injection or autohemotherapy alone. This combined method was soon discontinued because of reactions and lack of results. However, data concerning the small group receiving it are incorporated in this report because all the patients received injections of whole blood on the same schedule as did the larger group.

Thirteen patients received pituitrin injections and autohemotherapy. These persons were treated daily, receiving injections of whole blood, of from 10 to 15 cc., every third day and 1 cc. of surgical pituitrin® (posterior pituitary solution in 1 cc. ampuls containing 20 pressor units) on the days between injections of blood. All obtained relief of pain in about the same length of time as did patients treated with autohemotherapy alone. In this small group there were no treatment failures.

REACTIONS TO TREATMENT

The group receiving posterior pituitary injection complained of pain at the site of injection. Some nausea and diarrhea were also encountered. Pregnancy contraindicates the use of posterior pituitary injection because of the medicolegal aspect in cases of abortion or stillbirth from any cause.

The larger group receiving autohemotherapy alone presented no contraindications to treatment. A few patients complained of painful hips and sore arms after treatment. No instances of chills and fever were recorded.

SUMMARY

Autohemotherapy was reported by Jones and Alden to act almost as a specific for the treatment of herpes zoster. This statement is substantiated by the results

obtained in the 141 patients in this report treated by autohemotherapy. It is a simple, effective method of treatment that is completely free of complications, regardless of age or physical condition of the patient.

Complete relief of pain was obtained in an average of 5.22 days. Severe pain had usually subsided before the second or third injection was given. Treatment was given every third day until the patient reported complete relief of pain.

Most textbooks do not even mention this type of treatment, and a very complicated surgical procedure, paravertebral procaine block, was reported by Findley and Patzer.[6] Combined treatment gave no better results than did autohemotherapy alone.

CONCLUSIONS

The results of autohemotherapy in 154 cases of herpes zoster are reported.

Cure was obtained in all but 4 cases, and in these the patients subsequently recovered.

No reactions or contraindications to treatment were encountered.

Autohemotherapy is suggested as a simple routine procedure in the treatment of herpes zoster.

1230 Nix Building (5).

6. Findley, T., and Patzer, R.: Treatment of Herpes Zoster by Paravertebral Procaine Block, J. A. M. A. **128**:1217 (Aug. 25) 1945.

SIMPLE APPARATUS FOR CLINICAL PHOTOGRAPHY

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There has long been a need for a device by means of which the clinician can take photographs in color of various small lesions about the body without becoming entangled in great expense or cumbersome apparatus. The dermatologist, proctologist and general surgeon, especially, should find simplified clinical photography advantageous particularly for teaching purposes.

By means of the apparatus about to be described excellent kodachrome® transparencies of any cutaneous lesion, postoperative wound or pathologic condition which appears on the surface may be taken with a minimum of effort and expense.

As pictured (fig. 1) there is a transverse 15 inch (38 cm.) bar of aluminum, square in cross section and hollow, at each end of which is fastened a socket to hold a number 1 photoflood lamp in an ordinary matte reflector. Slots are placed as shown to permit the affixion of any camera, although the kodak bantam® is recommended as particularly suited to this work. The transverse bar is perforated at a right angle by an 18 inch (45.7 cm.) aluminum rod calibrated in inches. The position of this rod is adjustable so that the camera may be focused at any predetermined distance from the subject.

My practice being limited to proctology, I find that a 5½ by 8 inch (14 by 20.3 cm.) field is usually satisfactory and is attained by the use of a number 3

Portra® lens at 10 inches (25 cm.). In order for the picture to be taken, the apparatus is plugged into an ordinary wall socket; the lights are turned on; the tip of the focusing rod is touched to the skin just below the lesion to be photographed, and the cable release is pressed.

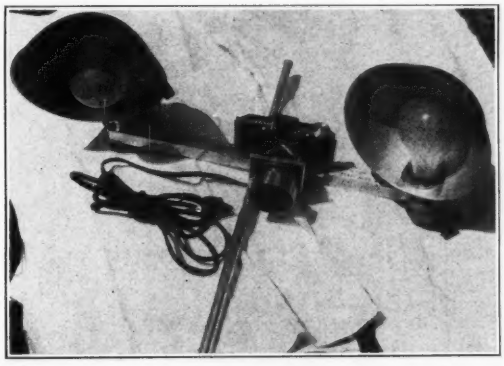

Fig. 1.—Photograph of apparatus.

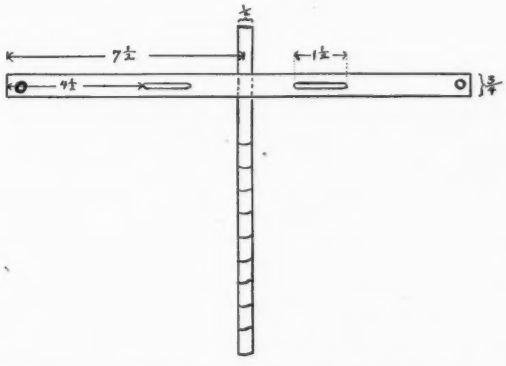

Fig. 2.—Diagram of apparatus. Measurements shown are given in inches, as are calibrations on the focusing rod.

The following figures will serve as a basis for calculating exposure data. Once the proper setting for the individual apparatus has been determined, the settings may be left constant and pictures snapped at will.

Lens opening.....f. 6
Time of exposure .....1/25 second
Distance from lens to subject .....10 inches
Camera (number 3 Portra® lens) ....focused at 3½ feet (106 cm.)
Size of field..... ....5½ by 8 inches (14 by 20.3 cm.)

131 Fulton Avenue.

News and Comment

GENERAL NEWS

Volume 3 of "Collected Studies of Skin Diseases" Still Available.—The Barnard Free Skin and Cancer Hospital has 300 copies of volume 3 of "Collected Studies of Skin Diseases," which was published during the war. The hospital was unable to send it to all dermatologists because many of them were in the service at the time of publication. The volume is now available, to those who have not received a copy, on request to the hospital, and copies will be mailed on a "first come, first served" basis.

Editors of Society for Investigative Dermatology.—At the June 1949 meeting of the Society for Investigative Dermatology, Dr. Naomi M. Kanof was appointed chairman of the editorial board. Dr. Marion B. Sulzberger was named chief editorial consultant. Manuscripts and inquiries should be addressed to the Editorial Office at 1150 Connecticut Avenue N.W., Washington 6, D. C.